U.S. ENVIRONMENTAL PROTECTION AGENCY
OFFICE OF RESEARCH AND DEVELOPMENT

U.S. EPA'sORD Children's Environmental Health (CEH) Research Roadmap 2015-2018

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Appendices (separate document)

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I. Executive Summary

EPA's Office of Research and Development's (ORD's) National Research Programs (Air, Climate, and Energy; Safe and Sustainable Water Resources; Sustainable and Healthy Communities; Chemical Safety for Sustainability; Human Health Risk Assessment; and Homeland Security - http://www2.epa.gov/epa-research/strategic-research-action-plans) are aligned on the core principle of sustainability and are designed to provide the solutions the Agency and the nation need to meet today's complex environmental and human health challenges. Inevitably, important scientific issues arise that cut across these six programs. Rather than create additional research programs for every cross-cutting issue, ORD is developing Research Roadmaps to clearly identify the science questions and associated research efforts that are ongoing in the six programs. These Roadmaps identify scientific gaps that inform the National Research Programs in the development of their Strategic Research Action Plans. As new, high priority, cross-cutting issues emerge, ORD expects to use this approach to integrate existing research efforts and identify needed work. Specific research products/deliverables are not included in the Roadmap: these may change as a result of ORD's planning and budgeting each year. However, ORD will use the EPA's website to provide details regarding research products/associated with implementation of this Roadmap. This Roadmap is devoted specifically to the issue of children's environmental health (CEH).

Sustainable decisions and actions are those that improve the wellbeing of individuals and communities today without compromising the health and welfare of future generations. The current EPA Administrator has *committed "to engaging closely with states, tribes, local partners, federal agencies and business and industry leaders in the most pragmatic, collaborative and flexible way possible to achieve environmental benefits for our children and future generations." (EPA Strategy)* To meet this commitment, the Agency and stakeholders require information, and tools to incorporate consideration of early lifestage sensitivity, susceptibility and vulnerability to support sustainable decisions and actions.

Today, there is increasing public awareness and concern around prevalence of children's health outcomes in the United States and a desire to understand potential role of environmental factors. Recent high visibility research publications have identified associations between environmental factors and risk of diseases including asthma, autism spectrum disorder, and childhood obesity. To date, research in this area has been limited and complexity of the exposures, disease etiology, and health outcomes, make it difficult to evaluate and interpret associations with exposures to environmental factors. However, as a result of high profile reports of links between increase in prevalence of CEH and environmental factors including air pollution and chemicals in consumer products, the public is looking toward the Agency to address or mitigate these environmental factors. While evidence is building of important links between CEH and environmental factors, the science in many cases is still far from actionable. More efficient, effective approaches are needed to develop understanding of the biological basis of complex environmental disease to support intervention and prevent effects.

The challenge is to evaluate emerging scientific evidence and fill gaps required to identify key environmental factors related to CEH where the Agency can take action. Specifically what are modifiable environmental factors that are practically amenable to change using available technologies, policies, and preventive and public health measures. Within this context, CEH research is conducted by the U.S. EPA Office of Research and Development to inform, support, and evaluate: regulatory decisions protective of children's health now and in the future; community decisions that protect and promote children's health across generations; and, ecological decisions that provide sustainable healthy environments for children. The goal is to enable and extend the Agency's ability to take actions that

minimize early-life exposures for optimal wellbeing across all developmental lifestages from preconception through puberty and into adulthood, recognizing that adverse consequences of exposure may not manifest until later in life.

ORD is investing heavily in children's environmental health research – intramural, extramural, and through strategic partnerships. Through our National Research Programs (Air, Climate, and Energy; Safe and Sustainable Water Resources; Sustainable and Healthy Communities; Chemical Safety for Sustainability; Human Health Risk Assessment; and Homeland Security) ORD is collecting and compiling data on children's exposures, and providing access to information on exposure factors, human behavior, chemical use, and developmental toxicity. Complex systems models of development are being constructed for tissues and multi-organ pathways. Studies are being conducted that combine epidemiologic and laboratory-based approaches to provide a holistic understanding of the relationship between early-life environmental exposures and wellbeing across the life span. ORD is developing tools and models that can be used to access data, forecast exposures for thousands of chemicals, and evaluate dosimetry of chemicals in the developing organism. ORD is also developing decision-support tools to help States, local governments, and community organizations consider potential impacts of environmental exposures in the context of decisions designed to protect and promote children's health.

Despite the many contributions to CEH research by ORD over the last decade, important gaps remain in actionable science and information required to understand, prevent, and mitigate impacts to children from **real-world** exposures to air, water, and chemicals. ORD leadership is required to bring together the science generated outside the Agency together with targeted information generated by EPA to build predictive capacity to evaluate alternative actions and to anticipate outcomes.

Working in conjunction with our partners in the EPA regulatory program and other EPA stakeholders, we identified four cross-cutting research areas required to address the critical science challenges in CEH facing the Agency:

(1) Knowledge infrastructure to address the problem that information and data are distributed and difficult to access;

(2) Systems understanding of the relationship between environmental exposures and health outcomes across development;

(3) Methods and models to evaluate early lifestage-specific risks and to support decisions protective of all lifestages;

(4) Translational research and tools to support community actions and decisions.

Transforming the Agency's capacity for considering child-specific vulnerabilities requires that ORD apply advanced systems science and integrate diverse emerging data and knowledge in exposure, toxicology, and epidemiology to improve understanding of the role of exposure to environmental factors during early life on health impacts that may occur at any point over the lifecourse.

This Children's Environmental Health Research Roadmap helps to connect the dots among the research activities being implemented across the National Research Programs. In addition, the vision articulated in this Roadmap serves to focus ORD investment in CEH research on areas where EPA can play a significant leadership role and to ensure this cross-cutting research is integrated and the results are impactful.

The impact of integrated ORD research in CEH will be that the:

- Agency has the data it needs to evaluate risks: Information on early lifestage exposure and hazard is collated and organized to provide accessible data that can be used to estimate important CEH factors and to support evaluation of risks.
- Agency has scientific basis for action: Systems understanding of early life exposures and associated health outcomes is used to build predictive models that enable effective Agency actions to protect the health of children.
- Agency has tools to evaluate benefits of alternatives and support decisions: Evaluated, accessible tools enhance agency capacity to adequately consider children's unique susceptibilities and vulnerabilities in Agency risk-based evaluations and sustainable public health decisions.
- Agency can enable communities to take action: Information and translation tools are developed to support Agency, State, Tribal, and local decision maker with the knowledge needed to manage risks and to protect and promote CEH.

EPA has a unique mandate to understand the role of exposure to modifiable exogenous environmental factors during early life, in the context of important modifying factors (i.e., non-chemical stressors), on health impacts across the course of development. This roadmap presents ORD's vision for providing integrated, cutting-edge science on CEH to inform Agency decisions. This roadmap will build stronger bridges to EPA partners and stakeholders who care about Children's Environmental Health issues. Resulting research will provide the science required for EPA actions to promote Children's Environmental Health and Wellbeing.

II. Introduction

A. Background

The mission of the EPA is to protect human health and the environment. In addressing health risks, the goal is to not only provide protection for the general population, but specifically for vulnerable individuals and groups, including children. In addition, the Agency expects that decisions and actions designed to promote and protect children's health should do so sustainably. That is, public policy for improving the health of individuals and communities should provide effective solutions today without compromising the health and welfare of future generations.

In the Fiscal Year 2014-2018 EPA Strategic Plan, the Agency "recognizes environmental justice, children's health, and sustainable development are all at the intersection of people and place. These goals are not mutually exclusive. Throughout all our work to achieve more livable communities, EPA is committed to ensuring we focus on children's health and environmental justice." (U.S. Environmental Protection Agency, 2014h). As such, ORD has identified children's health as a cross-cutting research area.

Over the last few decades there have been a number of key legislative and policy initiatives that have been crucial for EPA's mission to protect children's health. In response to concern about the potential vulnerability of children to dietary exposure of pesticides, the U.S. Congress requested that the National Academy of Sciences (NAS) study this critical public health issue. In 1993, the NAS released a report entitled Pesticides in the Diets of Infants and Children that described significant differences in toxicity and exposure of pesticides between children and adults (National Academy of Sciences, 1993). The NAS recommended that changes be made in regulatory practice. "Most importantly, estimates of expected total exposure to pesticide residues should reflect the unique characteristics of the diets of infants and children and should account also for all non-dietary intakes of pesticides. … Determinations of safe levels of exposure should take into consideration the physiological factors that can place infants and children at greater risk of harm than adults."

The NAS study led Congress to enact the Food Quality Protection Act (FQPA) in 1996, which significantly amended the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) and the Federal Food Drug, and Cosmetic Act (FFDCA) and set a new risk standard of ensuring "reasonable certainty of no harm." Effective protection of children was emphasized through EPA's use of an extra ten-fold children's safety factor when establishing tolerances unless data were available to show that a different factor was protective. The NAS report also provided the impetus for a series of actions within EPA and across the federal government to address the importance of assessing children's environmental health internally within EPA and across the federal government.

Since the 1990s, EPA has enacted a number of policies and strategies to protect children's health. In 1995 (and reaffirmed in 2013), EPA adopted its **Policy on Evaluating Health Risks to Children** (U.S. Environmental Protection Agency, 1995) to consider the risks to infants and children consistently and explicitly as a part of assessments generated during the decision making process, including the setting of standards to protect public health and the environment. In 2000, ORD released its **Strategy for Research on Environmental Risks to Children** (U.S. Environmental Protection Agency, 2000) to strengthen the scientific foundation of EPA risk-based assessments and risk management decisions that support children's health and welfare. In 2006, EPA prepared its Guide to Considering Children's Health When Developing EPA Actions: Implementing Executive Order 13045 and EPA's Policy on Evaluating

Health Risks to Children (U.S. Environmental Protection Agency, 2006). This guidance outlines the key steps in developing actions where children's health should be considered.

Table 1 presents a summary of the major laws, policies, and guidance on the protection of children's health from environmental hazards. Policies of the U.S. government (executive and legislative branches), US EPA and other federal agencies, US States and international organizations are considered.

Table 1. Key governmental and international actions on children's environmental health

Organization	Year	Title	Content
		U.S. Government	
Presidential Task Force (co-chaired by HHS and EPA)	1997	Presidential Executive Order 13045 – Protection of Children from Environmental Health Risks and Safety Risks and establishment of The Presidential Task Force on Environmental Health and Safety Risks to Children. (http://www.gpo.gov/fdsys/pkg/FR-1997-04-23/pdf/97-10695.pdf)	Requires all federal agencies to assign a high priority to addressing health and safety risks to children, coordinate research priorities on children's health, and ensure that their standards take into account the special risks to children.
	2001	HUD Announces $67 Million in Grants to Fight Childhood Lead Poisoning (http://archive.hhs.gov/news/press/2001pres/20011024a.html)	One of the task force's priorities was to examine programs that combat childhood lead poisoning.
	2012	Released the Coordinated Federal National Action Plan to Reduce Racial and Ethnic Asthma Disparities (http://www.epa.gov/childrenstaskforce)	The goal is to reduce disparities in the burden caused by asthma, particularly among children.
	2013	Established a Federal Healthy Homes Workgroup and released "Advanced Healthy Housing – A Strategy for Action." (http://www2.epa.gov/children/presidential-task-force-environmental-health-and-safety-risks-children)	One goal is to support research that informs and advances healthy housing in a cost-effective manner.
	2014	Established a Subcommittee on Climate Change, co-chaired by NIEHS, EPA, and DHS. (http://www2.epa.gov/children/presidential-task-force-environmental-health-and-safety-risks-children)	In July 2014, the Subcommittee hosted an Expert Consultation on the Effects of Climate Change on Children's Health to explore these issues and to help inform an ongoing U.S. Global Change Research Program.
106th U.S. Congress	2000	Children's Health Act (Public Law 106-310) (http://www.gpo.gov/fdsys/pkg/PLAW-106publ310/pdf/PLAW-106publ310.pdf)	Directed NIH, NIEHS, CDC, and EPA to conduct a National Children's Study.
110th U.S. Congress	2007	Energy Independence and Security Act of 2007	Required EPA to develop school siting guidelines and school environmental health guidelines.
		EPA	
	1995	Policy on Evaluating Health Risks to Children (U.S. Environmental Protection Agency, 1995) (http://www2.epa.gov/children/epas-policy-evaluating-risk-children-0)	The risks to infants and children should be considered consistently and explicitly as part of risk assessments, including the setting of standards to protect public health and the environment.

Organization	Year	Title	Content
	1996	National Agenda to Protect Children's Health from Environmental Threats (http://www2.epa.gov/children/epas-national-agenda-protect-childrens-health-environmental-threats)	All standards should be protective of heightened risks faced by children; develop a scientific research strategy regarding child-specific environmental threats; develop new policies regarding exposures faced by children.
	1996	Enactment of The Food Quality Protection Act (http://www.epa.gov/pesticides/health/children-standards.html)	Improved the safety standards that EPA uses in evaluating pesticide risks, especially risks to children.
	1997	Creation of the Office of Children's Health Protection (OCHP) (http://www2.epa.gov/children/history-childrens-environmental-health-protection-epa)	Mission is to make the health protection of children a fundamental goal of public health and environmental protection.
	1997	Creation of the Pediatric Environmental Health Specialty Units (PEHSUs) with ATSDR	PEHSUs translate research into public health and clinical practice, educate health providers and consult on pediatric environmental health issues.
	1998	Children's Environmental Health and Disease Research Centers (CEHCs) (Jointly funded with NIEHS) (http://epa.gov/ncer/childrenscenters/)	Explores ways to reduce children's health risks from environmental contaminants.
	2005 - 2008	New risk assessment guidance: Guidance on Selecting Age Groups for Monitoring and Assessing Childhood Exposures to Environmental Contaminants (U.S. Environmental Protection Agency, 2005a) (http://www.epa.gov/raf/publications/guidance-on-selecting-age-groups.htm); Supplemental Guidance for Assessing Susceptibility from Early-Life Exposure to Carcinogens (U.S. Environmental Protection Agency, 2005b)(http://www.epa.gov/raf/publications/cancer_guidelines/sup-guidance-early-life-exp-carcinogens.htm); A Framework for Assessing Health Risk of Environmental Exposures to Children (U.S. Environmental Protection Agency, 2006b) (http://cfpub.epa.gov/ncea/risk/recordisplay.cfm?deid=158363); Child-Specific Exposure Factors Handbook (U.S. Environmental Protection Agency, 2008) (http://cfpub.epa.gov/ncea/risk/recordisplay.cfm?deid=199243) (The latest information on child-specific exposure factors can be found in the 2011 Exposure Factors Handbook)	Risk assessment guidance for assessing childhood environmental health issues.
	2010	Working for Environmental Justice and Children's Health (part of EPA's Strategic Plan, 2011-15) (http://www.epa.gov/planandbudget/strategicplan.html	Emphasis on development and use of the latest science on children's unique vulnerabilities.
	2013	Protections for Subjects in Human Subjects Research with Pesticides (http://www.epa.gov/oppfead1/guidance/human-test.htm)	Provides for additional protection of susceptible subpopulations and prohibits EPA-sponsored research involving intentional exposures of pregnant women or children to any environmental substance. Implementation of this guidance has broad implications for children's environmental health research.

Organization	Year	Title	Content
	2013	ORD establishes six integrated, transdisciplinary National Research Programs: Air, Climate and Energy (ACE); Safe and Sustainable Water Resources (SSWR); Sustainable and Health Communities (SHC); Chemical Safety for Sustainability (CSS); Human Health Risk Assessment (HHRA); Homeland Security (HS) (http://www2.epa.gov/aboutepa/about-office-research-and-development-ord)	Provides the scientific foundation, methods, and tools that EPA needs to fulfill its mission of protecting human health and the environment.
	2013	EPA's 1995 Policy on Evaluating Health Risks to Children is reaffirmed by EPA's current Administrator (http://www2.epa.gov/sites/production/files/2013-11/documents/childrens_enviromental_health_risk_2013_reaffirmation_memorandum.pdf)	"This reaffirmation strengthens EPA's commitment to leadership in children's environmental health as well as the leadership of the Office of Children's Health Protection … and continues to encourage much needed research…"
Report on Environment	2014	EPA's Report on Environment (http://www.epa.gov/roe/)	Provides the best available indicators of national trends in the environment and human health and includes children's environmental health metrics.
Other Federal Agencies, Countries, and International Organizations			
NIH	2014	NIH announces a notice of intent to fund the Children's Health Exposure Analysis Resource (CHEAR); a National Exposure Laboratory Network (http://grants2.nih.gov/grants/guide/notice-files/NOT-ES-15-007.html)	Laboratories will provide a comprehensive suite of laboratory-based analytical services for samples from children's health studies.
FDA	2010	Advancing Regulatory Science for Public Health (http://www.fda.gov/downloads/scienceresearch/specialtopics/regulatoryscience/ucm228444.pdf)	Identifies improving child health as one of the major areas in which advancement in the field can improve public health.
HUD	2009	The Healthy Homes Strategic Plan (http://portal.hud.gov/hudportal/HUD?src=/program_offices/healthy_homes)	Roadmap in the protection of the health of children and other sensitive populations in a comprehensive and cost-effective manner.
Canada	2010	National Strategic Framework on Children's Environmental Health (http://www.hc-sc.gc.ca/ewh-semt/pubs/contaminants/framework_children-cadre_enfants/index-eng.php#a0)	Guides the development of action plans for the protection of children living in Canada from exposure to environmental hazards.
European Union	2013	The Helix Project (http://www.projecthelix.eu/)	A collaborative project using novel tools and methods to characterize early life exposure to a wide range of environmental hazards and which will be integrated and linked with data on major child health outcomes.
World Health Organization (WHO)	2004	Children's Environment and Action Plan for Europe (http://www.euro.who.int/__data/assets/pdf_file/0006/78639/E83338.pdf)	Developed four regional priority goals and committed the member states to develop and implement national children's environment and health action plans.

Organization	Year	Title	Content
	2012	State of the Science of Endocrine Disrupting Chemicals (http://www.who.int/ceh/publications/endocrine/en/)	Presents scientific knowledge on exposure to and effects of endocrine disrupting chemicals.
	2013	Guidance on identifying important lifestages for monitoring and assessing risks from exposures to environmental contaminants (http://www.who.int/ceh/publications/exposures_environmental_contaminants/en/)	Presents a harmonized set of age bins for monitoring and assessing risks from exposures to chemicals for global use that focuses on preconception through adolescence.
		States	
California	2001	Prioritization of Toxic Air Contaminants - Children's Environmental Health Protection Act (http://oehha.ca.gov/air/toxic_contaminants/SB25finalreport.html)	Presents information on chemicals that are identified as toxic air contaminants that may cause infants and children to be particularly susceptible to illness.
Washington	2008	Chemicals of High Concern to Children - Children's Safe Product Act (http://www.ecy.wa.gov/programs/swfa/cspa/)	Presents information on chemicals that are toxic and have either been found in children's products or have been documented to be present in human tissues.
Minnesota	2014	Chemicals of Special Concern to Children's Health (http://www.health.state.mn.us/divs/eh/children/chemicals.html)	Presents information on chemicals that may adversely affect children's health.

Current Drivers for CEH Research

There are three key drivers that define the need for, and focus of, EPA-led CEH research: 1) EPA's 2014-2018 Strategic Plan, 2) EPA program office mandates, and 3) Recent and emerging scientific findings related to CEH issues.

EPA's 2014-2018 Strategic Plan

The EPA Strategic Plan released in early 2014 calls specifically for applied research in CEH under two of the five strategic goals: Goal 3, Cleaning-Up Communities and Advancing Sustainable Development; and Goal 4, Ensuring Safety of Chemicals and Preventing Pollution.

In the area of cleaning up communities, research to enhance the ability to adequately consider children's unique susceptibilities and vulnerabilities will provide the Agency, State, Tribal, and local decision makers with the knowledge needed to make smart, systems-based decisions that will inform a balanced approach to their cleanup and development needs. EPA's chemical safety research will provide the scientific foundation to support safe and sustainable use of chemicals, including the systems understanding needed to adequately protect the health of children and other vulnerable groups.

Although there is no direct call for applied research in CEH under Goal 1 (Addressing Climate Change and Improving Air Quality) and Goal 2 (Protecting America's Waters), Agency decisions and actions to meet these strategic goals require the information and tools to consider child-specific vulnerabilities.

In addition, the EPA Strategic Plan emphasizes the importance of leveraging and building on existing partnerships to achieve strategic objectives. This includes partnering "with research organizations and academic institutions to focus and advance basic research and create models and measures to expand

the conversation on environmental and human health concerns to address priority-focused, locally based problems, specifically including … children's environmental health issues." (U.S. Environmental Protection Agency, 2014h).

EPA Program Office Drivers

EPA program offices have a variety of different mandates to protect children from environmental health risks. These mandates are based on authorities established under the environmental statutes and on guidance specific to each program office.

Office of Children's Health Protection (OCHP): EPA established OCHP in May 1997 to make the protection of children's health a fundamental goal of public health and environmental protection in the United States. OCHP supports and facilitates Agency efforts to protect children's health from environmental threats through participation in: regulation and standards development; risk assessment guidance and policy development; research planning; and outreach and partnerships with health care professionals, youth groups, and community groups. Important OCHP projects have included: EPA's Clean, Green, and Healthy Schools Initiative (http://www.epa.gov/schools/); increasing environmental health literacy of students and educators; support of Pediatric Environmental Health Specialty Units (http://aoec.org/pehsu/index.html); and publication (in partnership with the Office of Policy) of "America's Children and the Environment" (http://www.epa.gov/ace/), which evaluates and communicates trends in environmental contaminants that may contribute to childhood disease.

OCHP also provides children's health expertise in Agency rulemakings and other actions, including the Integrated Risk Information System (IRIS) and many other programs across the Agency. Data and analytical tools from ORD are valuable to OCHP's cross-cutting involvement in these priority actions for children's health.

Office of Chemical Safety and Pollution Prevention (OCSPP): The Toxic Substances Control Act (TSCA) provides EPA with the authority to require reporting, record-keeping and testing requirements, and restrictions related to chemical substances and/or mixtures. OCSPP carries out these requirements by reviewing new and existing chemicals, evaluating chemical hazard, including hazard relevant to developmental and reproductive toxicological endpoints, and exposure, including exposures of children to environmental chemicals. EPA is currently working with Congress, and members of the public, the environmental community, and industry to reauthorize TSCA. EPA is working with these groups to modernize and strengthen the tools available under TSCA to prevent harmful chemicals from entering the marketplace and to increase confidence that those chemicals that remain are safe and do not endanger the environment or human health, especially for consumers, workers, and children.

Recently, as part of EPA's approach to enhance the Agency's existing chemicals management program, OCSPP identified 83 chemicals (TSCA Workplan Chemicals) for further assessment under TSCA (http://www.epa.gov/oppt/existingchemicals/pubs/workplans.html). These chemicals were selected based on five criteria: hazard, exposure, persistence, bioaccumulation, and use, including use in children's products.

OCSPP also regulates all use of pesticides in the US based on legislative authority provided under the Federal Insecticide and Rodenticide Act (FIFRA). EPA's current pesticide review processes also focus on ensuring that pesticide registrations comply with the Endangered Species Act and achieve broader Agency objectives for water quality protection. The review processes place emphasis on the protection

of potentially sensitive populations, such as children, by reducing exposures from pesticides used in and around homes, schools, and other public areas.

The 1996 Food Quality Protection Act directed EPA to develop a screening program, using appropriate validated test systems and other scientifically relevant information, to determine whether certain substances including pesticides may have hormonal effects in humans. At the same time, the 1996 amendments to the Safe Drinking Water Act authorize EPA to screen substances that may be found in sources of drinking water for endocrine disruption potential. To carry out this directive, OCSPP established the Endocrine Disruptor Screening Program (EDSP) where EPA is using a two-tiered screening and testing process to gather information needed to identify endocrine-active substances and take appropriate action, as mandated by Congress. In 2005, EPA began screening priority chemicals under this program including: pesticide active ingredients and high production volume chemicals used as inert ingredients in pesticide formulation; drinking water contaminants, such as halogenated organic chemicals; persistent chemicals such as dioxins, and flame retardants; and chemicals found in plastics, pharmaceuticals and personal care products (http://www.epa.gov/endo/pubs/prioritysetting/index.htm). In 2010, OCSPP announced plans to make better use of computational toxicology tools in the EDSP and developed the EDSP21 workplan. This workplan outlines an approach for using computational or *in silico* models and molecular-based high-throughput assays to prioritize and screen chemicals to determine their potential to interact with the estrogen, androgen, or thyroid hormonal systems. (http://www.epa.gov/endo/pubs/edsp21_work_plan_summary%20_overview_final.pdf).

Office of Water (OW): In the standard setting process for chemicals in drinking water, OW is required, under Section 103 of the 1996 Amendments to the Safe Drinking Water Act, to determine "the effects of the contaminant on the general population and on groups within the general population such as infants, children, pregnant women, the elderly, individuals with a history of serious illness, or other subpopulations that are identified as likely to be at greater risk of adverse health effects due to exposure to contaminants in drinking water than the general population."

OW considers the effect of contaminants upon children's health in the standard setting process by following EPA's guidance on children's health issues: "Supplemental Guidance for Assessing Susceptibility from Early Life Exposure to Carcinogens" (http://www.epa.gov/raf/publications/cancer_guidelines/sup-guidance-early-life-exp-carcinogens.htm) and "A Framework for Assessing Health Risks of Environmental Exposures to Children" (http://cfpub.epa.gov/ncea/risk/recordisplay.cfm?deid=158363). OW uses these guidances in its qualitative assessment of the adverse health effects of contaminants, and for carcinogens, OW factors in age-dependent susceptibility in its dose-response assessment.

Office of Air and Radiation (OAR): In conducting risk assessments for air toxics, OAR routinely seeks to identify the highest risks to those groups—such as children—that may be more vulnerable to certain environmental contaminants than are adults. Such assessments are conducted for all air toxics rulemakings, including National Emissions Standards for Hazardous Air Pollutants (NESHAPS, otherwise known as Maximum Achievable Control Technology or MACT standards) and Residual Risk rules. During these assessments, OAR specifically estimates risks to children and/or determines if children are disproportionately affected by their exposures and/or behavioral patterns. OAR uses dose-response values which specifically account for the differential sensitivity of children as compared to adults and has developed exposure estimates for mutagenic carcinogens (e.g., vinyl chloride and polycyclic

aromatic hydrocarbons) which specifically account for the greater vulnerability of children to these compounds during their developmental years, based on EPA's "Supplemental Guidance for Assessing Susceptibility from Early Life Exposure to Carcinogens" (http://www.epa.gov/raf/publications/cancer_guidelines/sup-guidance-early-life-exp-carcinogens.htm).

OAR also carefully considers impacts on children's health as part of the periodic reviews of the national ambient air quality standard (NAAQS), in which the Agency must consider whether the standards are requisite to protect public health, including the health of at-risk subgroups, with an adequate margin of safety. Evaluating the effects of criteria air pollutants in children has been a central focus in several recent NAAQS reviews, including reviews of the lead, ozone, and particulate matter standards, which resulted in revised standards to strengthen public health protection.

Office of Solid Waste and Emergency Response (OSWER): OSWER provides policy, guidance and direction for the Agency's waste and clean-up programs, emergency response, the management of hazardous substances and waste, and the redevelopment of contaminated sites. OSWER implements its mission under a variety of mandates, including the Comprehensive Environmental Response, Compensation and Liability Act (CERCLA), the Resource Conservation and Recovery Act (RCRA), and Brownfields Revitalization Act. In addressing this mission, OSWER works to understand and protect the health of populations, taking into account unique susceptibilities and vulnerabilities of children.

OSWER directly considers potential impacts to sensitive subpopulations, including children in its risk assessment and risk management actions. Consistent with the National Contingency Plan [40 CFR 430(e)(2)(i)(A)(10], OSWER's cleanup under Superfund actions ensure that exposures to the human population, including sensitive groups, are without adverse effect during a lifetime or part of a lifetime, incorporating an adequate margin of safety. The Risk Assessment Guidance for Superfund (RAGS) documents provide specific guidance on the incorporation of child specific factors, including body weight, timing of exposure, and unique exposure pathway considerations, such as dust and soil intake rates.

Regional Offices: Each Regional Office has a Children's Environmental Health coordinator that is responsible for leading the Children's Environmental Health Program in their region, and to engage with the other regional coordinators, including Regional School Coordinators and risk assessors. These programs are based on national and regional strategies to protect children's environmental health through a number of regulations and voluntary programs. While exposures can occur in any number or variety of locations, the regions work with decision-makers to understand and reduce exposures in home, learning and play environments.

Scientific Drivers Related to Adverse Health Outcomes

Recent and emerging research findings on the relationship of environmental contributions to children's health outcomes are important drivers for EPA's CEH research. Evidence points to associations between early life exposure to environmental contaminants and a wide range of children's health outcomes including adverse birth outcomes, asthma, neurodevelopmental disorders, metabolic disease and childhood cancer.

Adverse birth outcomes: include preterm birth, low birth weight, neonatal mortality, and birth defects. Birth defects are seen in approximately 3% of births in this country while low birth weights are observed in 11% of births. In 2012, black non-Hispanic women had the highest rate of preterm birth of all racial

groups (16.8%). Adverse birth outcomes are leading causes of infant mortality and may presage long-term problems include motor, cognitive, visual, hearing, behavioral, and social-emotional problems.

Birth outcomes have been associated with exposure to a variety of environmental contaminants *in utero* and early in life including fine particulate matter (Dadvand et al., 2013; Fleischer et al., 2014; Stieb, Chen, Eshoul, & Judek, 2012) and chemicals such as arsenic (Boekelheide et al., 2012), organochlorine pesticides, organic solvents, and other air pollutants (Gorini, Chiappa, Gargani, & Picano, 2014).

Asthma: The incidence and severity of childhood asthma continues to rise. In 2009, asthma affected 7.1 million (about 10%) of children in the United States. Asthma disproportionately impacts minority children, especially in urban communities typified by low income, high levels of air pollution, and poor indoor air quality (Akinbami et al., 2012). 12.2% of children in families below the poverty line were reported to have asthma compared to 8.7% of children in families above the poverty line. A higher percentage of Black non-Hispanic children (16%) and children of "all other races" (12.4%) were reported to have asthma, compared to White non-Hispanic children (8.2%).

More is known about environmental factors that exacerbate asthma severity than those that cause asthma, but recent evidence implicates air pollution as a causative factor. Substantial evidence has associated *in utero* or early life exposures to environmental tobacco smoke, ambient and indoor air pollutants, and inhaled allergens (dust mites, pets and pollens) with asthma incidence and/or severity in children (Dick, Doust, Cowie, Ayres, & Turner, 2014; Selgrade, Blain, Fedak, & Cawley, 2013). Genetic factors and gene-environment interactions also play a role in asthma causation (Rigoli et al., 2011). Children with specific gene variants were shown to be at increased of asthma associated with air pollution (Macintyre et al., 2014). Environmental exposures may also impact asthma risk through epigenetic mechanisms, an emerging area of study (Kabesch, 2014; Salam, Zhang, & Begum, 2012).

Neurodevelopmental disorders: Developmental disabilities (DDs) including lower IQ, learning deficits and other indicators of poor cognitive function, and adverse effects on behavior, are common: about 1 in 6 children in the United States are affected. Between 1997 and 2008, the prevalence of DDs increased 17.1% impacting about t 1.8 million more children. Prevalence of autism increased 289% while ADHD increase 33%. Again, lower income children are disproportionally impacted by DDs. Children insured by Medicaid had nearly two-fold higher prevalence compared to those with private insurance.

Neurotoxicants that have been associated with developmental effects include lead, methylmercury, PCBs, arsenic, toluene, manganese, fluoride, chlorpyrifos, and tetrachloroethylene (Grandjean & Landrigan, 2014). Limited evidence is emerging to suggest an association between exposure to a range of environmental contaminants including air pollutants, organophosphate pesticides, brominated flame retardants, phthalates, bisphenol A, and perfluorinated compounds and adverse neurodevelopmental effects (Bellinger, 2013; Choi, Sun, Zhang, & Grandjean, 2012; Rodriguez-Barranco et al., 2013; Yim, Harden, Toms, & Norman, 2014).

Recent children's cohort studies implicate prenatal exposure to polycyclic aromatic hydrocarbons (PAHs) from air pollution and bisphenol-A with attention problems, anxiety and aggressive behavior in boys (F. Perera et al., 2012; F. P. Perera et al., 2011). The possible link between environmental contaminants and increasing prevalence of attention deficit hyperactivity disorder and autism is an area of active investigation. In addition, potential for gene-environment interactions are being studied. (Hu, 2012).

Metabolic Syndrome: Metabolic syndrome, a cluster of adverse health effects, including obesity, altered lipid levels, and other metabolic abnormalities, is increasing globally. Prevalence of childhood obesity in the U.S. has recently stabilized at approximately 16%. 22% of Mexican-American and 20% of Black non-Hispanic children are obese, compared with 14% of White non-Hispanic children. Prevalence of obesity is greater in children with family incomes below poverty level than in those above. The rise in obesity and related metabolic disease is of particular concern because the risk of life-threatening diseases, such as diabetes, cardiovascular disease, and cancer is increased in persons with metabolic disease.

The possibility that environmental chemicals can influence childhood obesity is currently an area of significant study. Chemicals that are under investigation include: dioxins, PCBs, DDT, DDE, perfluoroalkyls, PBDEs, phthalates, bisphenol A, organotins, lead, air pollution, polycyclic aromatic hydrocarbons (PAHs), naphthalene, diethylstilbestrol, thiazolidinediones. Some of these chemicals have been shown to increase obesity in laboratory animals and *in vitro* studies have shown cell differentiation that may indicate an association between certain chemicals and obesity (Karoutsou & Polymeris, 2012; La Merrill & Birnbaum, 2011; Scinicariello & Buser, 2014). Epigenetic reprogramming is hypothesized to be a contributing factor in childhood obesity and metabolic syndrome, and is an area of intense study (Janesick & Blumberg, 2011).

Developmental Origins of Disease: More generally, an increasing number of studies are addressing the hypothesis that exposure in early life to environmental stressors may influence development that impacts later health and disease risk. An area of intense interest involves epigenetic modification resulting from exposures during critical windows of development. The support for epigenetic change in early life comes from a large number of animal studies and a small number of observational studies in humans (Saffery & Novakovic, 2014). Evidence has been published for epigenetic changes including DNA methylation, histone modifications, and miRNAs in developmental programming, leading to an increased risk of disease (Bernal & Jirtle, 2010; Hou, Zhang, Wang, & Baccarelli, 2012; Vaiserman, 2014). Environmental compounds being studied for their ability to cause epigenetic changes include asbestos, benzene, endocrine-disrupting compounds, and metals (Kim, Bae, Na, & Yang, 2012; Vaiserman, 2014).

B. Purpose

Protecting children's health from environmental risks remains a critical and enduring part of EPA's mission. EPA conducts and supports CEH research to inform regulatory decisions and to support community decision-making to promote sustainable healthy environments for children. Given recent advances in the science of risk assessment, it has now become an opportune time to re-examine and update EPA's path forward for critical CEH research.

The purpose of this CEH Roadmap is to describe EPA's strategic vision for CEH research, building upon and extending the problems and needs identified in EPA's 2000 research strategy. This new vision aims to use all science, particularly 21st Century science and systems approaches to: improve our understanding of how environmental factors affect children's health and contribute to the most prevalent diseases and disorders; incorporate basic human health research into the development of innovative new approaches for assessing risks associated with early lifestage exposures, including prenatal and lactational exposures; and translate basic and applied research findings to inform new ways by which the Agency and others can take action to prevent or reduce adverse children's

environmental health outcomes and promote sustainably healthy environments in communities where children live, play and learn.

The ORD cross-cutting Research Roadmaps are not intended to be new research strategies for Strategic Research Action Plans (StRAPs). Rather, they take a cross-cutting look at existing and imminent ORD research portfolios and emerging StRAPs for each National Research Program (NRP) and describe the focus of ongoing research and the direction of the planned research. They also inform future research planning in relevant NRPs. As such, this cross-cutting Research Roadmap has two important attributes: 1) the research needs described are "owned" by an NRP and articulated as either existing or planned (definitively or aspirationally) in a near-term timeframe; and 2) research needs described are those for which EPA/ORD needs to play a transformative leadership role.

This Roadmap is focused specifically on CEH research. There is a separate Roadmap for research on environmental justice which will articulate research and needs specific to all lifestages, and highlight research that addresses both CEH and environmental justice (health disparity) concerns.

The lifestage scope of the research described in this Roadmap specifically considers impacts associated with exposure during or across developmentally sensitive windows. Although many reference are made to children as a "subpopulation" (e.g., 1996 SDWA amendments uses the term "subpopulation" to describe groups with unique attributes, including those defined by age or lifestage), since 2005 EPA has recognized the importance of distinguishing between population groups that form a relatively fixed portion of the population (e.g., groups based on ethnicity) and lifestages or age groups that are inclusive of the entire population. The term "lifestage" refers to a distinguishable time frame in an individual's life characterized by unique and relatively stable behavioral and/or physiological characteristics that are associated with development and growth. Thus, childhood should be viewed as a sequence of lifestages, from birth, through infancy and adolescence. EPA has official guidance defining early lifestage specific age bins which has been affirmed by WHO (Cohen Hubal et al., 2013; U.S. Environmental Protection Agency, 2005). **Error! Reference source not found.** outlines these lifestages which are the specific focus for this Roadmap and cross-cutting CEH research. Note that while exposures from preconception through adolescence are of primary interest, impacts may extend throughout the lifecourse into adult lifestages and across generations. Here the lifecourse is depicted as a circle to convey the concept of intergenerational impacts from environmental exposures.

The purpose of this roadmap is to describe and facilitate integrated ORD CEH research that will provide the Agency and stakeholders with scientific understanding, information, and tools required to address early lifestage sensitivity, susceptibility and vulnerability for sustainable decisions and actions.

III. Research Scope

A. Expanded Problem Statement

Sustainable decisions and actions are those that improve the health of individuals and communities today without compromising the health and welfare of future generations. **The U.S. EPA and**

stakeholders require scientific understanding, information, and tools to incorporate consideration of early lifestage sensitivity, susceptibility and vulnerability for sustainable decisions and actions.

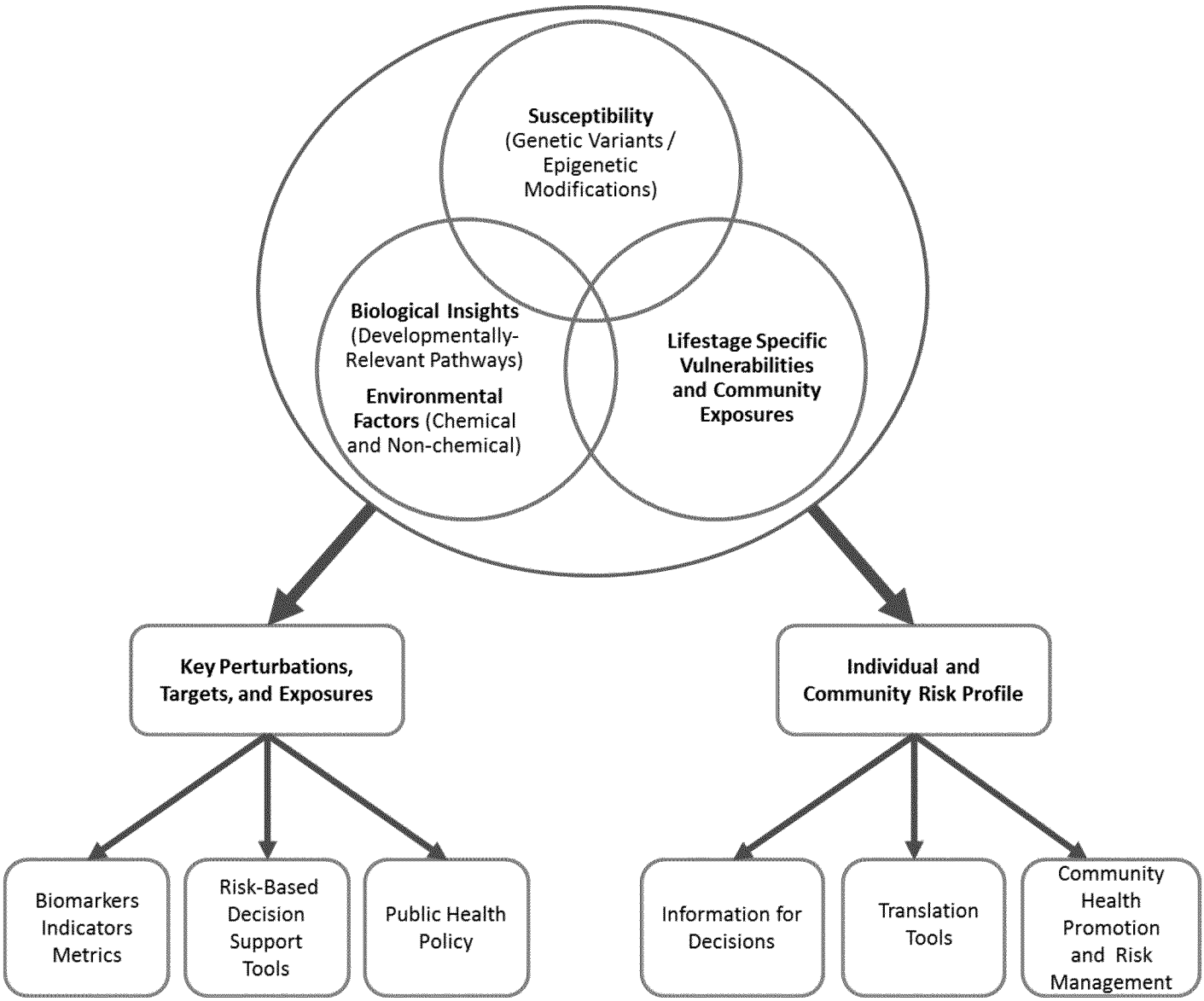
Within the broad sphere of children's environmental health, EPA has a unique mandate to focus on understanding the role of exposure to modifiable xenobiotic environmental factors during early life, in the context of important modifying factors (i.e., non-chemical stressors), on health impacts over the course of a lifetime. Specifically, applied research is required to enable and extend the Agency's ability to take action. The science challenges associated with filling this unique niche in CEH research are significant.

The Agency and stakeholders make decisions at several levels of organization; from the individual to community level all the way to the state and national level. ORD research will provide required information and tools by considering the different types of decisions and actions required to support CEH. The CEH research translation framework presented in Figure 1 captures the important science challenges addressed by ORD CEH research within this context. Two general translation route are depicted: one focused on providing cutting-edge science for effective public health policy and efficient risk management at the national level; the second at the community level.

Understanding of developmental biology, impacts to biological pathways resulting from perturbations at critical window of development, and genetic and environmental factors that may produce and/or modify these perturbations forms the scientific basis for both translation routes. In the first, identification of toxicity pathways coupled to identification of important environmental factors (exposures) provides new opportunities to anticipate impacts by considering early indicators of adversity and monitoring for emerging environmental contaminants. Information and tools along this translation route will inform decision making and public health protection at the population level. Decision support tools developed along this route may include: (1) biomarkers, metrics, and indicators for measuring and monitoring environmental exposures as well as providing early indication of toxicological impacts; and (2) models for risk-based decision making, informed by detailed understanding of relevant environmental stressors and associated perturbations to toxicity pathways. In the second translational route, knowledge of individual patterns of exposure and disease predisposition resulting from the full range of community-level determinants provides opportunities to develop community-based approaches to health promotion and risk management. Here, information and decision support tools are developed to inform and support actions by communities to manage risks and promote health by providing a clear understanding of important exposures and how these can be locally controlled.

Considerations of individual variation based on genetic susceptibility, lifestage, timing of exposures, and interaction of non-chemical stressors is required context for both routes and for holistic assessment of risk factors associated with complex environmental disease. By capturing the science challenges of characterizing biologically relevant exposure, the framework presented in Fig. 2 facilitates translation of advances and findings in computational toxicology to information that can be directly used to support risk-based decisions to improve public health. In addition, this framework captures the challenge of addressing data gaps along all levels of biological organization (i.e., from molecular through population levels) in a systems-based fashion to optimize design of future exposure and epidemiology studies. Such a strategic implementation of toxicology, exposure and epidemiology research is required to ensure efficient use of resources committed to children's health studies.

ORD research is designed and implemented through case examples that allow for demonstration and evaluation of research products. ORD works with EPA program partners and regions through our six



National Research Programs: to identify useful case examples; to develop and demonstrate the research products fit-for-purpose; and to evaluate the value added of ORD information and tools to both inform decisions and to support measurement of impact resulting from those decisions.

Figure 1. Children's Environmental Health Research Translation Framework (adapted from (Cohen Hubal et al., 2010))

B. CEH Research Areas

Working in conjunction with our partners in the EPA regulatory program and other EPA stakeholders, we identified four cross-cutting research areas required to address the critical science challenges in CEH facing the Agency. To provide the science, information and decision support tools required to promote and protect children's health and wellbeing, EPA's CEH research is designed to address the following four priority research areas:

(1) Knowledge infrastructure to address the problem that information and data are distributed and difficult to access

(2) Systems understanding of the relationship between environmental exposures and health outcomes across development

(3) Methods and models to evaluate early lifestage-specific risks and to support decisions protective of all lifestages

(4) Translational research and tools to support community actions and decisions

For each of these research areas, this Roadmap provides the general scope of the area, key research questions, and specific research needed to provide the answers.

Research Area 1: Knowledge infrastructure to address the problem that information and data are distributed and difficult to access

Information and data required to support Agency and stakeholder decisions and actions to promote and protect children are distributed and may be difficult to access. Much of these data are generated outside the Agency but are critical for: evaluating emerging scientific evidence for role of key environmental factors in CEH; identifying data gaps required to reduce uncertainties in model predictions; and providing effective decision support tools. In all cases, the knowledge systems to facilitate integration and analysis of CEH data are required to identify and protect susceptible lifestages.

Key research questions addressed in this research area:

- What data and information are most critical for characterizing early lifestage vulnerabilities and susceptibility in the areas of exposure, toxicokinetics, toxicodynamics, and disease etiology;
- What data and information are most critical for evaluating linkages between early life environmental exposures and health outcomes, including those that may appear later in life.
- What data and information are most critical for reducing early lifestage-related uncertainties in exposure and risk characterization to provide the basis for EPA's policy decisions?

Anticipated integrated impact:

Agency has the data it needs to evaluate risks. Information on early lifestage exposure and hazard is collated and organized to provide accessible data that can be used to estimate important CEH factors and to support evaluation of risks.

Research Area 2: Systems understanding **of the relationship between environmental exposures and health outcomes across development**

A holistic understanding of the factors that impact children's health, specific to each stage of development, is needed in order to attribute, reduce and eliminate risks specific to the environmental exposures over which EPA has regulatory authority. Systems level understanding of the relationship between environmental exposures and health outcomes across development is required to develop predictive models that enable effective Agency decisions and actions that protect susceptible lifestages. EPA CEH research is designed to develop this understanding by considering exposures to chemicals and chemical classes of concern as well as the influence of non-chemical stressors and the built environment on children's health outcomes. Toxicological and epidemiological studies on exposure to chemical and non-chemical stressors are included in this research area.
Key research questions addressed in this research area:

- By what common biological pathways do environmental contaminants contribute toward early origins of disease and to important childhood health outcomes, such as adverse birth outcomes, asthma, neurological disorders and metabolic syndrome?
- What are the key perturbations and biological targets associated with developmentally relevant adverse outcome pathways (AOPs)?
- What are the systems-level influences of the chemical and natural and built environments on these biological pathways and health outcomes?
- How can we evaluate the individual and community risk profiles associated with exposures to chemical mixtures including the contribution of non-chemical stressors across the course of development?

Anticipated integrated impact:

Agency has scientific basis for action. Systems understanding of early life exposures and associated health outcomes is used to build predictive models that enable effective Agency actions to protect the health of children.

Specific research to provide biological systems understanding of the relationship between environmental exposures and health outcomes across development:

- Identification of AOPS for chemicals that disrupt specific developmental processes.
- Evaluation of relevance/concordance of lab animal models for human health
- Linkage of environmental exposures to health outcomes via AOPs including outcomes apparent at birth and those which contribute to later onset of disease in childhood or adulthood.
- Development and evaluation of systems models to understand and predict developmental toxicity.
- Systems level understanding of the complex interactions between multiple chemical stressors and how these interact with non-chemical stressors (other environmental and socioeconomic factors), and genetics, including informing how those interactions may affect children's health.

Research Area 3: Methods and models to evaluate early lifestage-specific risks and to support decisions protective of all lifestages

Risk assessors and risk managers need methods to measure lifestage specific exposure, toxicity and health endpoints as well as model and tools to analyze and integrate the information to adequately consider lifestage specific factors in for sustainable decisions.

Key research questions:

- What methods, models and decision support tools are needed to allow the Agency to use all available data to inform risk-based decisions?
- What methods, models and decision support tools are needed to evaluate how and to what extent pregnant women and children are exposed to environmental stressors?
- What methods, models and decision support tools are needed to evaluate how associated health outcomes vary by specific early lifestages and exposure patterns?
- What methods, models and decision support tools are needed to support analysis of potential risks associated with exposures to multiple chemicals in the context of other important environmental stressors across development?

Anticipated integrated impact:

Agency has tools to evaluate benefits of alternatives and support decisions. Evaluated, accessible tools enhance agency capacity to adequately consider children's unique susceptibilities and vulnerabilities in Agency risk-based evaluations and sustainable public health decisions.

Specific models and methods to evaluate early lifestage specific risks and support regulatory decisions including:

- Efficient, cost effective methods for monitoring children's exposures.
- Tools for assessing exposure (timing and duration)-dose-response relationships in children including physiologically-based pharmacokinetic (PBPK) models that incorporate early life-stage specific parameters.
- Novel computational tools to incorporate estimates of developmental toxicity into risk assessments.
- Risk assessment tools for incorporating multiple exposures across multiple vulnerable stages to estimate risks that may accrue over time.
- Web-based tools that incorporate early lifestage-specific factors for predicting source-to-effects.
- Extend models and methods to estimate children's exposures at spatial and temporal scales relevant to the pollutant and health endpoint of concern.

Research Area 4: Translational research and tools to support community actions and decisions

Federal, State, Tribal and local governments make decisions at multiple scales (national to local) that impact children's health and wellbeing. Decision support tools that incorporate multiple factors about the built and natural environments that contribute to children's health, along with child-specific exposure and risk factors (including non-chemical stressors), can support informed decisions that protect and promote children's health in the communities where they live, learn, and play. Ideally, these tools should be developed through partnerships and active engagement with affected communities and suitable for use across geographic scales.

Key research questions:

- What are the real-world environmental exposures to children in their homes, schools and communities and how do they contribute to children's health risks?
- How do social and economic factors, including those specific to place, influence lifestage-specific exposure and risk?
- What tools can provide communities with the lifestage-specific information needed to support local decisions and actions?
- How can information regarding real-world environmental exposures to children inform community-based decisions in key sectors (e.g., land use; buildings and infrastructure; transportation; waste and materials management) to meet community needs?
- What are the most effective actions to prevent adverse environmental exposures and promote child wellbeing, how effective are these, and how can these be best communicated to communities and parents?

Anticipated integrated impact:

Agency can enable communities to take action. Information and translation tools are developed to support Agency, State, Tribal, and local decision maker with the knowledge needed to manage risks and to protect and promote CEH.

Specific research and tools to inform community decisions designed to protect and promote CEH:

- Methods and models for measuring or estimating exposures in pregnant women and children to environmental contaminants and potentially harmful substances in air, water, house dust, soil, and products encountered in their day to day lives.
- Models for estimating cumulative exposures and how they may vary in indoor vs. outdoor environments.
- Methods for measuring the sustainable benefits and costs of community decisions designed to promote CEH such as increasing green space or access to healthy foods.
- Community assessment tools (e.g., geographic information system (GIS) models) that identify sources of exposures as well as health-promoting factors with respect to specific places where children live, recreate, or attend school.
- Approaches for incorporating CEH into Health Impact Assessments.
- Approaches and guidance for optimizing the built environment to sustainably protect and foster CEH.

C. Research Alignment and Coordination

The four priority CEH Research Areas are cross-cutting to ORDs six National Research Program. Currently, each of the following NRPs strategically plans and conducts research in one or more of the four Research Areas: Air, Climate, and Energy (ACE); Chemical Safety for Sustainability (CSS); Human Health Risk Assessment (HHRA); Sustainable and Healthy Communities (SHC); and Safe and Sustainable Water Resources (SSW). Several of the NRPs conduct research in all four areas. Details of the research are described in the individual NRP Strategic Research Action Plans.

Modifiable environmental factors addressed by ORD research include chemicals/classes of current and emerging focus where the Agency has a role in setting policy or in developing regulatory actions. These include: manufactured chemicals and materials (pesticides, solvents, industrial chemicals, nanomaterials); hazardous chemicals released to the environment through improper waste disposal or

accidental releases to the environment; environmental contaminants resulting from human activities such as energy generation (air pollutants); and water disinfection. Across the NRPs, research is focused on providing systems understanding of the role of modifiable environmental factors to the childhood diseases and disorders prevalent today, including adverse birth outcomes, asthma, neurodevelopmental disorders, and metabolic outcomes. Table 2 summarizes the individual NRP contributions to the 4 research areas in the context of these prevalent CEH health outcomes:

In addition, to meet the Agency's mandate for protecting children, ORD relies heavily on strategic partnerships with dozens of organizations ranging from other federal agencies, state governments and international organizations, to academia, nongovernmental organizations and industry. All of the strategic partners have an interest in promoting and protecting children's health. Strategic partnerships are finalized through numerous types of agreements including STAR Grants, Cooperative Research and Development Agreements, Materials Transfer Agreements and Memorandum of Understanding.

One of ORD's leading partners in CEH research is NIEHS. Jointly EPA, through its STAR Grants program and NIEHS fund the Children's Environmental Health and Disease Research Centers. Currently, there are 16 active centers conducting research to increase understanding how environmental factors affect children's health and promote translation of basic research findings into intervention and prevention methods to prevent adverse health outcomes. Other important partnerships include those of the Association of Toxic Substances and Disease Registry (ATSDR), the Centers for Disease Control (CDC), the Department of Health and Human Services (DHHS), the Food and Drug Administration (FDA), the Department of Housing and Urban Development (HUD), and several institutes at the National Institutes of Health (NIH). These partnerships are critical for both conducting basic research are children's health as well as for implementing research focused on interventions that support CEH.

Table 2. CEH Research efforts as distributed across the four research areas.

	CHILDREN'S HEALTH OUTCOMES			
RESEARCH AREA	Adverse Birth Outcomes	Asthma	Neurodevelopmental Disorders	Metabolic Syndrome
Knowledge Infrastructure	CSS	HHRA	CSS, HHRA	CSS, HHRA
Systems Understanding	CSS, SHC, SSWR, ACE	SHC, ACE	CSS, SHC, ACE	CSS, SHC
Methods & Models	CSS, HHRA	ACE, HHRA	CSS, HHRA	CSS, HHRA
Community Decision Support	SHC, ACE	SHC, ACE	SHC	SHC

IV. Cross-Cutting ORD Research

A. Current ORD Research

This section summarizes ORD's current and recently completed research activities (2012-15) as they are aligned with the four CEH research areas described in Section III. These research activities are implemented by ORD's NRPs according to their respective StRAPs (http://www.epa.gov/research/research-programs.htm). Each activity addresses NRP-specific outputs and at the same time contributes to achieving the CEH Roadmap objectives. The NRP with key responsibility for each of the activities is provided in parentheses after the project name in this section, as follows:

- ACE = Air, Climate, and Energy Research
- CSS = Chemical Safety for Sustainability Research
- HHRA = Human Health Risk Assessment Research
- SHC = Sustainable and Healthy Communities Research
- SSWR = Safe and Sustainable Water Resources Research

See Appendix A for further details on the research activities outlined below, as well as information on additional ORD research activities; Appendix B for a summary of ORD published research on CEH outcomes from 2008 – 2014; and Appendix C for databases and tools that ORD has developed that include CEH information.

Current ORD activities in Research Area 1 (knowledge infrastructure) include the compilation of data on exposure factors, human behavior, chemical usage, and childhood physiological parameters, and the development of databases that provide the results of high throughput *in vitro* assays and *in vivo* studies. Under Research Area 2 (systems understanding), ORD is developing bioinformatics-based, adverse outcome pathway, and simulation models to evaluate the toxicity of environmental chemicals. In addition, Children's Research Centers and place-based studies are evaluating the relationship between exposure and a variety of health outcomes in children and adolescents, leading to an increased understanding of how interactions among complex stressors may increase the sensitivity of children. Research Area 3 (methods and models) includes the development of exposure assessment tools and human exposure models for environmental chemicals. ORD is developing dosimetry models and using new approaches to categorize lifestages and to evaluate chemical mixtures. Under Research Area 4 (translational research), ORD is developing decision support tools to enable communities to provide healthy environments for children. ORD is also translating research findings on children's health to inform communities and other local groups as they develop environmental health related strategies that are sustainable.

Research Area 1: Knowledge infrastructure to address the problem that information and data are distributed and difficult to access

Currently, knowledge resources are being developed under Research Area 1 in the following three areas: A) exposure information, B) early lifestage pharmacokinetic parameters, and C) developmentally relevant hazard data. ORD's relevant research in each of these areas is summarized as follows:

1.1 Exposure Information

Exposure data are critical for characterizing children's environments and for evaluating interactions of children with the environment across development.

1.1.1 Exposure Factors Handbook (HHRA)

Data about children's exposures and exposure factors, such as lifestage specific modeled estimates of soil and dust ingestion is incorporated into EPA's Exposure Factors Handbook (U.S. Environmental Protection Agency, 2011); available at http://cfpub.epa.gov/ncea/risk/recordisplay.cfm?deid=236252. The exposure factors include: drinking water consumption, soil and dust ingestion, inhalation rates, dermal factors including skin area and soil adherence factors, consumption of fruits and vegetables, fish, meats, dairy products, and homegrown foods, human milk intake, human activity factors, consumer product use, and building characteristics.

1.1.2 Consolidated Human Activity Database (CHAD)

ORD's Consolidated Human Activity Database (CHAD) is a compilation of data on human behavior from 24 individual studies (U.S. Environmental Protection Agency, 2014d); available at: http://www.epa.gov/heasd/chad.html. This resource includes more than 50,000 individual data days of detailed location and activity data and corresponding demographic data including age, sex, employment, and education level. Data are included for all ages, including infants and children.

1.1.3 ExpoCast Database (CSS)

ExpoCast Database (ExpoCastDB) was developed to improve access to human exposure data from observational studies, including those funded by ORD. ExpoCastDB consolidates measurements of chemicals of interest in environmental and biological media collected from homes and child care centers. ExpoCastDB is available as a searchable database (U.S. Environmental Protection Agency, 2014g); available at: http://actor.epa.gov/actor/faces/ExpoCastDB/Home.jsp on EPA's Aggregated Computational Resource (ACToR) system, an online data warehouse that collects data on over 500,000 chemicals from over 1000 public sources (U.S. Environmental Protection Agency, 2014a); available at: http://actor.epa.gov/actor/faces/ACToRHome.jsp.

1.1.4 Chemical and Product Categories (CSS)

Chemical and Product Categories (CPCat) is a database of information on how chemicals are used (U.S. Environmental Protection Agency, 2014b); available at: http://actor.epa.gov/actor/faces/CPCatLaunch.jsp. CPCat contains information on the uses of chemicals (including use by children); products that contain chemicals; manufacturers of the products; and a hierarchy of consumer product "use" categories. It also contains information on any regulations or studies in which the chemical has been considered hazardous to children.

1.2 Early Lifestage Pharmacokinetic Parameters

Pharmacokinetic and pharmacodynamic parameters for all lifestages are required to predict the potential for health effects from exposures to environmental chemicals. Child-specific parameters are used to characterize dose to the developing child *in utero,* after birth through lactational exposure, and during early infancy through prepubertal ages.

1.2.1 Enzyme Ontogeny Database (CSS)

Chemicals are often biotransformed in the body by activating and/or detoxifying enzymes whose expression changes over time from the developing embryo to adulthood. Thus, metabolic capacity based on the spectrum and relative quantity of critical enzymes at different lifestages can play an important role in determining childhood susceptibility to environmental chemicals. ORD has developed an enzyme ontogeny database that is useful for the development of PBPK models to explore metabolism-based variability during early lifestages.

1.3 Developmentally Relevant Hazard Data

Data from *in vivo* animal studies, screening assays, and other study types are needed in order to carry out risk and hazard assessments on environmental chemicals. ORD has developed databases that allow for easy access to developmental hazard data that is being used to link environmental exposures at early lifestages with health outcomes in children and later in life.

1.3.1 ToxCast Database (CSS)

ToxCastDB provides results of high throughput *in vitro* assays. Biology covered in the large set of assays include endpoints related to endocrine, reproductive, and developmental toxicity and a major proportion of the assays are human-based cells or proteins. ToxCastDB is available as a searchable database through the ACToR system (U.S. Environmental Protection Agency, 2014i); available at: http://actor.epa.gov/actor/faces/ToxCastDB/Home.jsp.

1.3.2 Toxicity Reference Database (CSS)

Toxicity Reference Database (ToxRefDB) contains data from thousands of *in vivo* animal studies and is available as a searchable database through the ACToR system (U.S. Environmental Protection Agency, 2014j); available at: http://actor.epa.gov/toxrefdb/faces/Home.jsp. Developmental toxicity data includes results from studies on more than 380 chemicals with 18 endpoints for both the rat and rabbit, while the reproductive toxicity information is based on the results from multigenerational reproductive studies on 316 chemicals, with 19 parental, reproductive, and offspring endpoints.

1.3.3 Adverse Outcome Pathway Wiki (CSS)

An Adverse Outcome Pathway (AOP) is a conceptual framework that portrays existing knowledge concerning the linkage between a direct molecular initiating event and an adverse outcome. The goal of an AOP is to provide the framework to connect the two events. AOP Wiki is a wiki-based tool that provides an interface for collaborative sharing of established AOPs and building new AOPs (Anonymous, 2014); available at: http://aopkb.org/aopwiki/index.php/Main_Page. AOP Wiki uses templates to make it easier for users to include the information needed for proper evaluation of an AOP. Developmentally relevant AOPs are being incorporated. Currently endocrine pathways are well represented.

Research Area 2: Systems understanding of the relationship between environmental exposures and health outcomes across development

Research Area 2 has been divided into the following two subgroups: A) systems biology to predict developmentally relevant outcomes and B) systems understanding of complex stressors. ORD's relevant research in each of these areas is summarized as follows:

2.1 Systems Biology to Predict Developmentally Relevant Outcomes

Systems models for tissues and multi-organ pathways specific to embryo-fetal and neonatal development are being developed. These models increase our understanding of the biologic mechanisms of chemical stressors that contribute to childhood health outcomes.

2.1.1 Bioinformatics-Based Models (CSS)

As discussed in section 1.3.1, ToxCastDB uses high throughput biochemical and cellular *in vitro* assays to evaluate the toxicity of environmental chemicals. The development of predictive models is being carried out in phases, with the development and publication of first-generation (Phase I) ToxCast predictive models for reproductive toxicity (M. T. Martin et al., 2011) and developmental toxicity (Sipes et al., 2011). Pathways for endocrine disruption (Reif et al., 2010), embryonic stem cell differentiation (Chandler et al., 2011) and disruption of blood vessel development (Kleinstreuer et al., 2011) have been linked to the Phase I ToxCast *in vitro* data. For the next ~700 compounds in Phase II, where animal toxicology is less well-characterized, ORD is developing plausible model structures that deal with the possibility of additional relevant interactions and components beyond those represented in the first-generation predictive models.

2.1.2 AOP Models (CSS)

ORD is developing AOP models, such as the vascular AOP model, with the aim of establishing the predictive value of chemical disruption of blood vessel development (vasculogenesis) during critical windows of embryonic and fetal development. A vasculogenesis model is being tested in Zebra fish embryos and in embryonic stem cells and as additional individual AOPs are developed, they can be assembled into AOP networks that may aid the prediction of more complex interactions and outcomes resulting from exposure to complex mixtures and/or chemicals with multiple modes of actions.

2.1.3 Simulation Models (CSS)

Simulation models predict chemical toxicity using relevant biologic information, such as the influence of subcellular pathways and networks on the development of tissues and organs. ORD is developing the Virtual Embryo model, a simulation model of predictive toxicology of children's health and development, which can be applied to prenatal or postnatal (including lactational) exposures.

2.2 Systems Understanding of Complex Stressors

Epidemiologic, animal studies, and *in vitro* assays are being used to develop a systems understanding of the relationship between environmental exposures as stressors and lifestage-specific susceptibility and vulnerability.

2.2.1 Laboratory Based Studies (CSS and SHC)

Intramural ORD research has used a variety of *in vitro* models to evaluate the effects of chemical exposure in developmentally relevant systems. Cell (e.g., human multipotent neuroprogenitors, rodent embryonic stem cells, specific pathway-responsive modified hepatocytes), organ (e.g., human and rodent palatal shelves), and whole rodent embryo cultures, as well as whole organisms (developing zebrafish) have been used to address issues of toxic response. Many of these models have been developed, characterized and refined to answer specific research questions. Several model systems have been used to evaluate the effects of chemicals to aid in the translation of high throughput data in the ToxCast assays. *In vitro* approaches using adipocyte stem cells are also being developed as potential predictors of obesity and to explore cellular mechanisms of action of specific chemicals.

Experimental research is also addressing causality in lifecourse (longitudinal) rodent studies where effects of early life exposures on postnatal development and multiple health outcomes can be evaluated under controlled laboratory conditions. These studies are also being used to examine the extent to which modifying factors such as diet, exercise and stress may alter sensitivity to chemical stressors, a question relevant to diverse community settings and conditions.

2.2.2 Epidemiologic Studies (SHC and ACE)

EPA-NIEHS Children's Environmental Health and Disease Prevention Research Centers (CEHC)

The EPA-National Institute of Environmental Health Sciences (NIEHS) jointly funded Children's Environmental Health and Disease Prevention Research Centers (CEHCs, or "Children's Centers") Program, ongoing since 1998, continues to generate exposure and biomarker data in pregnant women and children, along with mechanistic data in experimental models, in order to show relationships between exposure to chemical contaminants and a variety of children's health outcomes, and to identify critical windows of susceptibility (U.S. Environmental Protection Agency, 2014e); available at: www.epa.gov/ncer/childrenscenters; http://cfpub.epa.gov/ncer_abstracts/index.cfm/fuseaction/recipients.display/rfa_id/560/records_per_page/ALL. The long-range goals of this STAR Program include understanding how environmental factors affect children's health, and promoting translation of basic research findings into intervention and prevention methods to prevent adverse health outcomes (Table 3).

Table 3. Current EPA/NIEHS Children's Environmental Health and Disease Prevention Research Centers Exploring Associations Between Exposures and Health Outcomes in Children.

Institution – P.I.	Chemical Exposures and Other Stressors	Outcomes	Underlying Mechanisms (molecular, genetic, social factors)
Brown University – Boekelheide	Arsenic, EDCs (estradiol, BPA, genistein), dietary restriction	Fetal liver, lung and prostate development; prostate cancer in later life	Endocrine disruption; Epigenetic changes in organ development
Columbia University – Perera	Endocrine Disrupting Compounds (BPA), PAHs,	Neurodevelopmental disorders such as problems with learning and behavior; obesity and metabolic disorders	Endocrine disruption; Epigenetic reprogramming and metabolic syndrome
Dartmouth College – Karagas	Arsenic in drinking water and food	Growth and development; immune response	Epigenetic changes and influence of gut microbiome

Institution – P.I.	Chemical Exposures and Other Stressors	Outcomes	Underlying Mechanisms (molecular, genetic, social factors)
Duke University/ University of Michigan – Miranda	Environmental, social and individual susceptibility factors, PM, Ozone	Disparities in birth outcomes; respiratory health in infants	Social determinants of childhood disease
Duke University – Murphy	Environmental tobacco smoke	ADHD; neurobehavioral dysfunction	Epigenetic modulation in fetal and child development
Johns Hopkins University – Diette	Airborne pollutants (particulate matter, nitrogen dioxide), allergens, urban diets	Asthma	Dietary contributions to asthma ,based on anti-oxidant and anti-inflammatory impacts on immune function and inflammation
National Jewish Health – Schwartz, Szefler	Air pollution (ozone, PM, NO_2), ambient bacterial endotoxin	Asthma; immune system function; determinants of host defense	Host-immune responses and TL4 receptor function; interactions between ozone and endotoxin
University of California at Berkeley - Buffler, Metayer	Pesticides, tobacco-related contaminants, chemicals in housedust (PCBs, PBDEs)	Childhood leukemia	Epigenetic and genetic influences
University of California at Berkeley – Eskenazi	Pesticides (DDT, manganese), flame retardants	Neurodevelopment; growth and timing of puberty; obesity	Epigenetic reprogramming; altered endocrine status
University of California at Berkeley – Hammond, Balmes, Shaw	Ambient air pollutants (airborne PAHs), in utero exposure to traffic-related pollutants, endotoxin	Birth defects/preterm birth, immune system dysfunction (asthma/allergies), obesity/glucose dysregulation	Gene variants in biotransformation enzymes; molecular mechanisms e.g., altered T-cell function; neighborhood factors
University of California at Davis – Van de Water	BPDEs, pyrethroid insecticides, perfluorinated compounds, POPs	Autism spectrum disorder (ASD)	Immune dysfunction and autoimmunity; genetic/epigenetic contributions
University of California, San Francisco – Woodruff	EDCs, PBDEs (BDE-47), PFCs (PFOA), psychosocial stress	Placental and fetal development, adverse birth outcomes	Gene expression changes via epigenetic mechanism; contribution of psychosocial stress
University of Illinois at Urbana-Champaign – Schantz	EDCs (phthalates, BPB); high fat diet	Neurological and reproductive development	Endocrine disruption; oxidative stress
University of Michigan – Peterson, Padmanabhan	BPA, phthalates, lead, cadmium	Birth outcomes; child weight gain; body composition; activity patterns; hormonal levels; sexual maturation; metabolomics and risk of metabolic syndrome	Dietary influences; epigenetics and gene expression changes; oxidative stress
University of Southern California – McConnell	Near-roadway air pollution including elemental carbon, PM 2.5	Obesity; fat distribution; metabolic phenotypes; systemic inflammation	Expression of genes in metabolic pathways; beta cell function; oxidative stress;
University of Washington – Faustman	Agricultural pesticides	Altered neurodevelopment	Genetic susceptibility; neurotoxicity ; oxidative stress; cellular pathways underlying neurodevelopment

Clean Air Research Centers (ACE)

ORD's Clean Air Research Centers Program (STAR) includes a number of epidemiologic projects directly relevant to children's environmental health. Two currently active Centers are producing new data and knowledge on the relationship between air pollution and children's health, with final reports expected in 2015. The Center at Emory University is generating "Novel estimates of pollutant mixtures and pediatric health in two birth cohorts," and the Center at Harvard University is evaluating "Longitudinal effects of multiple pollutants on child growth, blood pressure and cognition." (U.S. Environmental Protection Agency, 2012); available at: http://www.epa.gov/ncer/quickfinder/airquality.html

Place-Based Studies (ACE and SHC)

ORD recognizes that combinations of stressors are often unique to a particular community setting and that interventions to improve children's health must take this complexity into account. For example, a STAR grant and ORD in-house project, "The Near-Road Exposures and Effects of Urban Air Pollutants Study (NEXUS)" (ACE) examined the influence of traffic related air-pollutants on respiratory outcomes in a cohort of 139 asthmatic children (ages 6-14) who lived close to major roadways in Detroit, Michigan. Another place-based study, "The Mechanistic Indicators of Childhood Asthma (MICA)" (SHC) study was designed to pilot an integrative approach in children's health research. MICA incorporates exposure metrics, internal dose measures, and clinical indicators to decipher the biological complexity inherent in diseases such as asthma and cardiovascular disease with etiology related to gene-environment interactions. Additionally, grantees are conducting place-based research such as exploring: interactions among stress and air pollution in community settings; how school conditions influence academic performance (SHC); and how to predict exposures for children living near a Superfund site (ACE).

Research Area 3: Methods and models to evaluate early lifestage-specific risks and to support decisions protective of all lifestages

Research Area 3 has been divided into the following two subgroups: A) exposure, and B) dosimetry models. ORD's relevant research in each of these areas is summarized as follows:

3.1 Exposure

ORD has developed tools to increase the usability and access to exposure data, models to predict exposure by a variety of pathways and routes, and approaches for categorizing lifestage changes and prioritizing chemical mixtures.

3.1.1 EPA ExpoBox (HHRA)

EPA ExpoBox is a web-based compendium of over 800 exposure assessment tools that provides links to exposure assessment databases, models, and references (U.S. Environmental Protection Agency, 2013c); available at: http://www.epa.gov/risk/expobox/docs/Expobox_Fact-Sheet_Nov13.pdf. It includes approaches for exposure assessments, tiers and types of exposure assessments, chemical classes, routes of exposure to chemicals, lifestages and populations, and exposure media. It also includes, in a searchable and downloadable format, the full list of exposure factors from the Exposure Factors Handbook (see section 1.1.1).

3.1.2 SHEDS-HT Model (CSS)

The Stochastic Human Exposure and Dose Simulation–HT (SHEDS-HT) model is a screening-level human exposure model for chemicals. Exposure results can also be estimated for individual age-gender cohorts. Exposure-relevant information specific to children included in SHEDS-HT includes age-specific behaviors (such as hand-to-mouth contact and use of consumer products), time spent in microenvironments, and food intakes.

3.1.3 ExpoCast (CSS)

ExpoCast is a rapid, high-throughput model using off the shelf technology that predicts exposures for thousands of chemicals (U.S. Environmental Protection Agency, 2014f); available at: http://epa.gov/ncct/expocast/. ORD research is generating and incorporating new information about age-dependent exposures (e.g., product use) into ExpoCast so that this model can be more specifically applied to capture children's unique vulnerabilities to support risk-based decisions.

3.2 Dosimetry Models

ORD has developed a number of dosimetry models that assess exposure, predict dose, and describe the kinetics of environmental chemicals as related to children's health.

3.2.1 Empirical Models (CSS)

Persistent Bioaccumulative Toxicants

A statistical model was developed for predicting levels of polybrominated diphenyl ethers (PBDEs) in breast milk, based on serum data from the National Health and Nutrition Examination Survey (NHANES) (Marchitti, LaKind, Naiman, Berlin, & Kenneke, 2013). In this research, congener-specific linear regression partitioning models were developed and applied to 2003-2004 NHANES serum data for U.S. women. These models provide a sustainable method for estimating population-level concentrations of PBDEs in U.S. breast milk and should improve exposure estimates in breastfeeding infants.

ORD is now applying this approach to other environmental chemicals (dioxins, perfluorinated compounds (PFCs), polychlorinated biphenyls (PCBs), and organochlorine pesticides). ORD is also working on developing a comprehensive quantitative structure-activity relationship (QSAR)-based model for predicting milk:serum partitioning ratios for classes of chemicals where serum and milk data are not available to construct regression models.

In vitro to In vivo Extrapolation

ORD has proposed an approach to link results from *in vitro* high throughput studies with population group-specific dosimetry for neonates, children, and adults, and exposure estimates (Wetmore et al., 2014). For nine ToxCast chemicals, pharmacokinetic models for multiple population groups were constructed that predicted chemical concentrations in the blood at steady state. These models have potential application to estimate chemical-specific pharmacokinetic uncertainty factors and to estimate population group-specific oral equivalent dose values to aid in chemical prioritization and identifying population groups with greater susceptibility to potential pathway perturbations.

3.2.2 PBPK Models

Virtual Embryo Project (CSS)

ORD has developed a life-stage PBPK model which has been incorporated into the Virtual Embryo project. This model was developed to computationally investigate the relationship between chemical exposure, tissue dosimetry and *in vitro* markers of critical events related to AOPs. The model includes time-changing physiological and biochemical descriptors related to a pregnant mother, fetal growth, and child exposure through lactation.

Ethanol (ACE)

To supplement and complete PBPK models in the literature, ORD developed PBPK models to describe the kinetics of ethanol in adult, pregnant, and neonatal rats for the inhalation, oral, and intravenous routes of exposure (S. A. Martin et al., 2012).

Research Area 4: Translational research and tools to support community actions and decisions

Research Area 4 has been divided into the following four subgroups: A) decision support tools, B) problem driven research, C) translational research, and D) social determinants of health. ORD's relevant research in each of these areas is summarized as follows:

4.1 Decision Support Tools

ORD is developing decision support tools for State, Tribal and local governments and other organizations in order to make sound decisions about both community development and healthful environments, and to avoid unintended consequences.

4.1.1 Community-Focused Exposure and Risk Screening Tool (SHC)

ORD has developed the Community Focused Exposure and Risk Screening Tool (C-FERST) (U.S. Environmental Protection Agency, 2013a); available at: http://www.epa.gov/heasd/c-ferst/, which has been developed as a "toolkit" for step-by-step community assessment guidance (e.g., Community Action for Renewed Environment (CARE) roadmap), GIS maps, reports, fact sheets, best practices, and potential solutions. Children's health issues in C-FERST currently include childhood lead exposure, childhood asthma, and schools. Recently, C-FERST was used, along with other tools, to inform a Health Impact Assessment (HIA) related to school renovation decisions in Springfield, Massachusetts.

4.1.2 EnviroAtlas (SHC)

EnviroAtlas, scheduled for public release in 2014 will include, at least for selected urban areas, such indicators as the locations of schools, recreational areas and factors relevant to health outcomes (demographics, income) and access to transportation routes and indicators of ecosystem services such as tree cover (related to heat, recreation, green-space accessibility). This tool also includes an Eco-Health Relationship Browser (U.S. Environmental Protection Agency, 2013b); available at: http://www.epa.gov/research/healthscience/browser/introduction.html. Health outcomes currently searchable in the browser of direct relevance to CEH include low birth weight and preterm birth, asthma, ADHD, and obesity.

4.2 Problem-Driven Research

Studies are being conducted to further the understanding of linkages between human health and environmental exposures. Communities are using results of these analyses to make decisions concerning renovation of schools, location of recreational areas, and future development.

4.2.1 EPA Pilot Study Add-On to the Third Study Site of the Green Housing Study (SHC)

The Green Housing Study is a collaborative effort between the U.S. Department of Housing and Urban Development (HUD) and the Centers for Disease Control and Prevention (CDC). In partnership with HUD and CDC, ORD will collect additional multimedia measurements and questionnaire data from the index children actively participating in the Green Housing Study and a sibling(s) in order to characterize personal, housing, and community factors influencing children's potential exposures to indoor contaminants at various lifestages.

4.2.2 Dust and soil ingestion (SHC)

ORD is using models to estimate different exposure parameters, such soil and dust ingestion rates, in children. For example, ORD used the SHEDS-Soil/dust model to estimate soil and dust ingestion rates for young children at two Taiwanese locations, and for simulations pertinent to U.S. children in specific age categories (Glen, Smith, & Van Der Wiele, 2013).

4.2.3 Chemical and Non-chemical Stressors and Childhood Obesity (SHC)

ORD is currently completing a state-of-the-science literature review to identify chemical and non-chemical stressors related to childhood obesity. Numerous chemical and non-chemical stressors were identified and grouped into the following domains: individual, family, community, and chemical. Data shows that there is not always a positive association with a stressor and childhood obesity, and that there can be inconsistent correlations between the same stressors and obesity. However, there is sufficient evidence to suggest the interactions of multiple stressors may contribute to the childhood obesity epidemic.

4.2.4 Chemical and Non-chemical Stressors and Neurocognitive Health (SHC)

ORD is conducting research to examine stressors related to neurocognitive health in children, ages 3-6 years. Key exposure factors were identified for each developmental lifestage from pregnancy to 3-6 years old. These elements were incorporated into a model and the results suggest that some childhood exposures (e.g., socioeconomic status, parent-child interaction, diet, built environment) not only present as key factors, but act as effect modifiers of stressors experienced during pregnancy and infancy (e.g., lead, pesticides, prenatal stress).

4.2.5 Community Multi-scale Air Quality Model (ACE)

The EPA's Community Multi-scale Air Quality (CMAQ) Model is a powerful computational tool used by EPA and states for air quality management that gives detailed information about the concentrations of air pollutants in a given area. Comparison of data from the CMAQ model with birth outcomes or childhood hospital admissions for asthma has generated data on associations between pollutant exposure (i.e., particulate matter (PM) or ozone) and health outcomes (U.S. Environmental Protection Agency, 2014c), available at: http://www.epa.gov/AMD/Research/RIA/cmaq.html.

See Appendix A for additional examples of problem-driven technical support and research on PCBs in Schools (HHRA) and Child-Specific Exposure Scenarios examples (HHRA).

4.3 Translational Research

Translational research involves translating the results from research on children's health into findings that are useful to communities, neighborhoods, health care providers, or other groups as they develop strategies to work on local environmental health issues.

4.3.1 EPA/NIEHS Children's Center Program (SHC)

As discussed in section 2.2.2, the EPA-NIEHS co-funded Children's Centers (CEHCs) Program is generating exposure and biomarker data in pregnant women and children, showing relationships between exposure and a variety of children's health outcomes, and identifying critical windows of susceptibility (U.S. Environmental Protection Agency, 2014e); available at: www.epa.gov/ncer/childrenscenters. A critical and unique component of the Children's Centers Program is the inclusion of Community Outreach and Translation Cores. These cores use a variety of innovative approaches to translate research findings and intervention strategies to community stakeholders (see Table 4).

Table 4. EPA/NIEHS Children's Centers Community Outreach and Translation – Community Partners.

Institution – P.I.	Study Site Location(s)	Community Outreach and Translation – with Community Partners
Brown University – Boekelheide	Providence, Rhode Island	Silent Spring Institute, Environmental Justice League of Rhode Island
Columbia University – Perera	New York City (Northern Manhattan and South Bronx), Poland, China	Bronx Borough Presidents Office, Bronx Health Link, Columbia Community Partnership for Health, Columbia University Head Start, Community Health Worker Network of NYC, Dominican Medical Association, New York, Harlem Children's Zone Asthma Initiative, Harlem Health Promotion, Northern Manhattan Perinatal Partnership, Nos Quedamos, WE ACT for Environmental Justice
Dartmouth College – Karagas	Hanover, New Hampshire	Dartmouth-Hitchcock Concord Clinic, Concord Hospital Family Clinic, Concord Obstetrics and Gynecology Professional Associates, Concord Women's Care, Family Tree Health Care (Warner, NH), Dartmouth Hitchcock Lebanon Clinic, Concord Hospital, The Family Place, Dartmouth-Hitchcock Medical Center, New Hampshire Department of Environmental Health Services, New Hampshire Birth Conditions Program, University of New Hampshire Department of Molecular, Cellular and Biomedical Sciences
Duke University/ University of Michigan – Miranda	Durham, North Carolina and Ann Arbor, Michigan	Durham Congregations, Associations, and Neighborhoods (CAN), Triangle Residential Options for Substance Abusers (TROSA), Durham Affordable Housing Coalition, Partnership Effort for the Advancement of Childrens Health/Clear Corps (PEACH), Durham People's Alliance, Durham County Health Department, Lincoln Community Health Center, Duke University Nursing School Watts School of Nursing, City of Durham Department of Neighborhood Improvement Services, City of Durham Department of Community Development, Children's Environmental Health Branch of NC Department of Environment and Natural Resources, North Carolina Asthma Alliance, East Coast Migrant Head Start, North Carolina Community Health Center Association, North Carolina Rural Communities Assistance Project

Institution – P.I.	Study Site Location(s)	Community Outreach and Translation – with Community Partners
Duke University – Murphy	Durham, North Carolina	DukeEngage Program, El Centro Hispano (local Latino community), Partnership for a Healthy Durham
Johns Hopkins University – Diette	Baltimore, Maryland	Baltimore City Head Start Program, Baltimore City Health Department Healthy Homes Program, Baltimore School Food Services Program, Healthy Stores Program, Maryland Asthma Control Program, Women Infants and Children (WIC) nutrition programs
National Jewish Health – Schwartz, Szefler	Denver, Colorado	Colorado Asthma Coalition, Colorado Clinical Guidelines Collaborative, Colorado Department of Public Health and Environment, Denver Public School System, Lung Association of Colorado, Rocky Mountain Prevention Research Center, EPA Region 8, Alamosa Public School, Denver Health, Colorado Public Health, Practice Based Research Network, Regional Air Quality Council, Colorado Air Quality Commission, Grand Junction Housing Authority, Western Colorado Math & Science Center, Region 8 Pediatric Environmental Health Specialty Unit (PEHSU)
University of California at Berkeley – Buffler, Metayer	Berkeley, California	Network of 8 clinical institutions in northern and central California participating in the Northern California Childhood Leukemia Study (NCCLS), national community of pediatric health care professionals with an interest in environmental health issues; national community of persons interested in leukemia; California community of persons interested in childhood leukemia; Region 9 Pediatric Environmental Health Specialty Unit (PEHSU)
University of California at Berkeley – Eskenazi	Berkeley and Salinas, California	Clinica de Salud del Valle de Salinas, Natividad Medical Center, South County Outreach Effort (SCORE), Monterey County Health Department, California Rural Legal Assistance (CRLA) Program, Grower/Shipper
University of California at Berkeley/ Stanford University – Hammond, Balmes, Shaw	Berkeley, Palo Alto, Bakersfield and San Joaquin Valley, California	Medical Advocates for Healthy Air, Fresno Metro Ministry, Center on Race, Poverty, and the Environment, San Joaquin Valley Latino Environmental Advancement Project (LEAP), El Comite para el Bienestar de Earlimart, Coalition for Clean Air, San Joaquin Valley Cumulative Health Impact Project (SJV-CHIP), Central California Environmental Justice Network, Central Valley Air Quality Coalition, Californians for Pesticide Reform
University of California at Davis – Van de Water	Davis, California	Families for Early Autism Treatment, Learning Disabilities Association, Parents Helping Parents, San Francisco Bay Chapter of the Autism Society of America, Alameda County Developmental Disabilities Council, Cure Autism Now, State of California health/developmental service providers, California Departments of Developmental Services and Health Services, California Regional Centers and Office of Environmental Health Hazard Assessment
University of California, San Francisco – Woodruff	San Francisco, California	American College of Obstetricians and Gynecologists (ACOG District IX), Association of Reproductive Health Professionals, Physicians for Social Responsibility (PSR) San Francisco Bay Area Chapter, WORKSAFE (California Coalition for Worker Occupational Safety & Health Protection), California Department of Health Occupational Health Branch
University of Illinois at Urbana-Champaign – Schantz	Urbana-Champaign, Illinois and New Bedford, Massachusetts	Illinois Action for Children (IAFC), American Academy of Pediatrics (AAP), Just-In-Time Parenting, Champaign-Urbana Public Health Department, Great Lakes Center for Environmental Health, Cambridge Health Alliance, Carle Foundation Hospital, Provena Covenant Medical Center

Institution – P.I.	Study Site Location(s)	Community Outreach and Translation – with Community Partners
University of Michigan – Peterson, Padmanabhan	Ann Arbor, Michigan and Mexico City, Mexico	Early Life Exposures in Mexico to Environmental Toxicants (ELEMENT), National Institute of Public Health, Mexico City, Detroit Hispanic Development Corporation
University of Southern California – McConnell	Los Angeles, California	The Children's Clinic (Long Beach and South Bay), Asian and Pacific Islander Obesity Prevention Alliance, East Yard Communities for Environmental Justice, Digital Rain Factory, Los Angeles Parks Foundation, The Trust for Public Land Center for Park Excellence, Policies for Livable, Active Communities and Environments (PLACE) of Los Angeles, Trade, Health and Environment Impact Project, Center for Community Action & Environmental Justice (Riverside and San Bernardino), Coalition for a Safe Environment (Wilmington), East Yard Communities for Environmental Justice (Commerce and East L.A.), Long Beach Alliance for Children with Asthma, Outreach Program of Southern California Environmental Health Sciences Center Los Angeles (USC/UCLA), Urban & Environmental Policy Institute, Occidental College
University of Washington – Faustman	Yakima Valley, Washington State	Community members in the Yakima Valley, Farm Workers Union, Growers' Association, Washington State Department of Health and Department of Agriculture, Farm Workers' Union, Yakima Valley Farm Workers Clinics, Radio KDNA (Spanish language), Washington State Department of Labor and Industries, Columbia Legal Services, Washington State Migrant Council, EPA Region 10

4.4 Social Determinants of Health (Place-Based Studies)

ORD is carrying out research on the biological, environmental, and social conditions that may contribute to disparities in health outcomes in children.

4.4.1 NIMHD Centers of Excellence on Environment and Health Disparities (SHC)

Social determinants of health are a focus of research in the *EPA- NIMHD Centers of Excellence on Environment and Health Disparities* (http://www.epa.gov/ncer/ehs/disparities/health-disparities.html). ORD, through an interagency agreement with the National Institute of Minority Health and Health Disparities (NIMHD) (http://www.nih.gov/about/almanac/organization/NIMHD.htm) is supporting the establishment of transdisciplinary networks of excellence in health disparities research to achieve a better understanding of the complex interactions of biological, social and environmental determinants of population health.

One of these Center projects, "Analysis and Action on the Environmental Determinants of Health and Health Disparities" (University of South Carolina) is exploring six areas of health disparities that contribute disproportionately to premature death and morbidity found among poor and racial/ethnic minorities (e.g., infant mortality). Another project, "Environmental Health Disparities Research" (University of Texas) is exploring the individual- and neighborhood-level contributions to disparities in children's pulmonary health.

4.4.2 Environmental and Community Factors Influence Effectiveness of Medical Treatments for Asthma (SHC)

An ORD study, in collaboration with the University of North Carolina, "Observational Assessment of Baseline Asthma Control as a Susceptibility Factor for Air Pollution Health Effects in African-American Children with Persistent Asthma", is examining factors that contribute to asthma disparities in adolescents. The study is following a cohort of African American youth with moderate-to-severe asthma and examining a variety of factors including air pollution, home environment, and community issues that may contribute to the high rate of asthma in this population and the relative effectiveness of medical treatments.

4.4.3 Integrated Approaches to Sustain the Built and Natural Environment and the Communities they Support (SHC)

In this study, researchers are using GIS tools and multi-layered mapping to examine relationships between access to green space and birth outcomes. Analyses focus on associations between birth measures across the greater Durham-Chapel Hill, North Carolina area and various measures of green space around the home, including tree cover along busy roadways.

Summary of ORD CEH Research Partnerships

ORD has partnered with a number of other Federal agencies and independent organizations to further CEH research. One example where EPA has reached out to leverage expertise and capacity in our partner federal agencies is on the topic of endocrine disruption. Evidence is mounting that some chemicals disrupt the endocrine system. The endocrine system regulates biological processes throughout the body and is sensitive to small changes in hormone concentrations. Some of this research has identified dose-response relationships that have nonmonotonic curves. Nonmonotonic dose-response curves (NMDRs) are of concern because they do not follow the usual assumption made in toxicology that as dose decreases the response also decreases. In addition, more complex interactions and outcomes resulting from exposure to complex mixtures and/or chemicals with multiple modes of action are not addressed well with existing models and assessment tools. Prenatal and early-life exposures are of particular concern and additional complexity is associated with the fact that these exposures may lead to health impacts across the lifespan. As a result, there is a need to shift thinking about how potential for adverse impacts and ultimately risk is evaluated. To comprehensively evaluate the evidence in this arena, EPA has formed a working group with experts from several EPA offices, FDA, NIEHS, and NICHD to explore this issue and to write a state of the science paper (U.S. EPA, 2014).

Table 5 lists some of ORD's partner organizations and the CEH programs that are currently underway through these partnerships.

Table 5. ORD Partnerships and Activities

Partners	Research	Description
NTP/NIEHS	Children's Environmental Health and Disease Research Centers (http://epa.gov/ncer/childrenscenters/)	Research to increase understanding how environmental factors affect children's health and promote translation of basic research findings into intervention and prevention methods to prevent adverse health outcomes.
NTP/NIEHS	Systematic review of progestin use during pregnancy (http://dx.doi.org/10.1289/ehp.1306711)	Systematic review of progestin use during pregnancy with interest on the effects in the mother and offspring after exposure during pregnancy/gestation.
NTP/NIEHS & NICHD; CDC	National Children's Study (http://www.nationalchildrensstudy.gov/Pages/default.aspx)	Multi-year research study examining the effects of environmental influences on the health and development of children.
ATSDR; Association of Occupational and Environmental Clinics	Pediatric Environmental Specialty Units (http://aoec.org/pehsu/aboutus.html)	Ten specialty units across the U.S. that are a source of medical information and advice on environmental conditions that influence children's health.
HUD; CDC	EPA Pilot Study Add-On to the Green Housing Study	Study that is collecting additional multimedia measurements and questionnaire data from the index children in the Green Housing Study and a sibling(s) in order to characterize personal, housing, and community factors influencing children's potential exposures to indoor contaminants at various lifestages.
CDC	National Birth Defects Prevention Study (http://www.nbdps.org/)	Population-based, case-control study examining the causes of birth defects.
NIH/National Institute of Minority Health and Health Disparities	STAR Centers of Excellence of Environment and Health Disparities (http://www.epa.gov/ncer/ehs/disparities/health-disparities.html)	Networks of excellence in health disparities research to achieve a better understanding of the complex interactions of biological, social and environmental determinants of population health.
DHHS, FDA, Health Resources and Services Administration, NIH, Office of the Assistant Secretary for Health, HUD, DOJ, and DOT	Interagency Asthma Disparities Workgroup (part of the President's Task Force on Environmental Health Risks and Safety Risks to Children) (www.epa.gov/childrenstaskforce)	Workgroup with the goal of reducing the burden caused by asthma, particularly among minority children and children with family incomes below the poverty level.
CAAT DNT workshop 2014	Center for Alternatives to Animal Testing (CAAT) workshop on developmental neurotoxicity testing http://caat.jhsph.edu/programs/workshops/DNT4/	Presented information on cutting-edge technologies being used to develop alternative tests for developmental neurotoxicity testing.

V. Research Gaps and Priority Research Needs

In the context of Agency mandates for CEH information (Section IIA), the decision context as presented in the Translation Framework (Figure 2), and a set of high visibility child health outcomes (Appendix D) identified by ORD and Program Partner members of the CEH roadmap working group, a gap analysis was conducted to identify and prioritize needs for ORD research in CEH.

The ORD portfolio of active and planned CEH research as described in the evolving NRP Strategic Research Action Plans was reviewed. Here a strong set of tools for addressing current regulatory mandates was identified. Gaps remain around specific needs for science and information to incorporate consideration of early lifestage sensitivity, susceptibility and vulnerability into these tools. Building confidence that EPA decisions are fully considering lifestage specific issues will require incorporating extant data and developing targeted information to reduce uncertainties in model predictions and risk-based assessments.

Emerging scientific understanding of CEH and the potential role of modifiable exogenous environmental factors was reviewed for a set of high visibility health outcomes. Prevalence and trends were summarized as was evidence pointing to associations between early life exposure to environmental contaminants and the following children's health outcomes: adverse birth outcomes, asthma, neurodevelopmental disorders, metabolic syndrome and childhood cancer. In addition, maturing scientific understanding of shared mechanisms for these complex environmental diseases (e.g., endocrine disruption) was considered. Building evidence in support of the Developmental Origins of Health and Disease hypothesis including implications of epigenetic effects (Saffery & Novakovic, 2014) was also identified as an important scientific driver for research in CEH as part of this gap analysis.

The scope of CEH research activities in other federal agencies was evaluated. NIH (including NIEHS and NICD) are making significant investments in research to increase the understanding of fundamental shared mechanisms of complex disease, genetic susceptibility across the lifespan to environmental diseases, and a broad range of other modifying factors, including psychosocial stressors (National Institute of Environmental Health Sciences, 2012). Based on this gap analysis, it is clear that rather than duplicate these investments, ORD will need to leverage these efforts and identify pivotal leadership role for EPA.

Clear gaps remain in actionable science and information required to understand, prevent, and mitigate impacts to children from **real-world** exposures to air, water, and chemicals. ORD leadership is required to bring together the science generated outside the Agency together with targeted information generated by EPA to build predictive capacity to evaluate alternative actions and to anticipate outcomes. This section highlights priority research needs identified for each of the four CEH Roadmap research areas. The bullet points present the strategic research gaps and the discussion provides examples of research needs and potential approaches to begin to address these needs.

Research Area 1: Knowledge infrastructure to address the problem that information and data are distributed and difficult to access

Early lifestage-specific data that could support Agency decisions are being generated at an increasing pace both within EPA and across the wider children's health research community. However, significant

barriers remain to effectively access and mine relevant information to understand and predict the role of exposures to environmental factors during early life on health impacts. Priority Agency needs in this research area are for:

- Accessible data on critical lifestage-specific factors that influence children's vulnerability and resilience to environmental insults, including efficient links to access/collate knowledge and data about such factors from research conducted across the wider CEH research community,
- Accessible information on lifestage-specific determinants of activities, behaviors, physiology and exposure,
- Accessible information on susceptibility to chemicals and other contaminants based on lifestage (absorption, distribution, metabolism, excretion (ADME), toxicity, and PBPK considerations),
- Associated data on genetic susceptibility and increased susceptibility due to health and nutritional status, including pre-existing diseases and disorders,
- Accessible lifestage-specific data for non-chemical stressors linked to the built and natural environments, and to social and economic factors,
- Accessible data and information that shows the inter-relationships between chemical exposures and factors modifying those exposures.

ORD can begin to address these gaps by leveraging current activities within the NRPs to apply advanced approaches for curating and providing access to data through high interest use-cases (i.e., research focused on addressing a gap in one or more of the other three research areas described in this Roadmap). For example, ORD has multiple activities focused on providing web-based information resources and associated web services to efficiently access these data (e.g., dashboards) as inputs to design workflows and analysis tools.

ORD has also developed a novel semi-automated approach using bioinformatics and computational techniques to mine the literature and facilitate systematic review. Using MeSH terms, ORD can find articles of interest and search in a systematic way. First, articles of interest are captured into a set database using specific MeSH annotations. The MeSH terms for this first pass are generally related to chemicals, proteins, or adverse outcomes of interest, but may include any MeSH terms. Second, this set of publications are queried using additional terms (e.g., proteins, cell-processes, species) to find articles where these terms are co-annotated. The co-annotation of terms gives plausible hypotheses about their associations, as well as the publication reference, without having to manually search the literature. Once these relationships and articles are identified, the article can be manually evaluated for evidence of this association. This database and mining approach is useful for identifying global hypotheses about associations of interest such as chemical-protein, chemical-cell process, or chemical-adverse outcome at all levels of biological complexity. These relationships can then be used to build AOPs, understand unappreciated connections, and identify current data gaps.

These approaches can be applied in the context of NRP- specific and cross-cutting ORD CEH research to amplify the impact of investments in studies, models, and decision support tools.

Research Area 2: Systems understanding of the relationship between environmental exposures and health outcomes across development

The NIH (including NIEHS and NICHD) is currently investing significant resources in research to increase our understanding of the fundamental shared mechanisms of complex disease, susceptibility across the

life span to diseases resulting from environmental factors, and links between the totality of environmental exposures and biological pathways (National Institute of Environmental Health Sciences, 2012). EPA's Strategic Plan translates this fundamental knowledge to provide a systems understanding that is necessary to adequately protect the health of children. As such, ORD can provide leadership in addressing priority gaps associated with using systems-based understanding of biology (from the molecular, tissue, and organ level out to the individual and population) to predict the potential for adverse impacts associated with development, chemical use, and environmental contamination. To effectively provide this leadership will require strategic implementation of ORD's STAR extramural grants program and leveraging of partnerships of other cross-agency partnerships. Priority gaps in this area are broad and include the need for:

- Improved understanding of critical environmental factors, and interactions, that impact children's growth and development at EPA-defined early lifestages (U.S. Environmental Protection Agency, 2005) and across the lifecourse.

- Understanding of the extent to which environmental stressors contribute to the childhood diseases and disorders prevalent today, including: abnormal birth outcomes (neonatal mortality, premature birth, morbidity, birth defects), metabolic and endocrine imbalance (associated with obesity and neurological outcomes), cognitive disorders related to neurodevelopmental dysfunction (learning problems, attention deficit hyperactivity disorder (ADHD), autism), and respiratory dysfunction such as asthma.

- Complex systems models that integrate key determinants to predict potential outcomes and impacts.

The Adverse Outcome Pathway (AOP) framework currently gaining traction in the toxicology and risk assessment communities provides an opportunity to integrate ORD CEH research across NRPs to begin to address these key gaps in the context of high priority assessment needs specific to early lifestages. An AOP portrays existing knowledge of linkage between a direct molecular initiating event and an adverse outcome at a biological level of organization relevant to risk assessment (i.e., actionable) (Ankley et al., 2010). These AOPs provide a framework for organizing and communicating existing knowledge concerning the linkage between molecular initiating events, intermediate key events along a toxicity pathway, and apical adverse outcomes traditionally considered relevant to risk assessment and/or regulatory decision-making. When developed and evaluated in a rigorous manner, AOPs provide a scientifically-defensible foundation for extrapolating from mechanistic data to predicted apical outcomes. Additionally, as individual AOPs are developed, they can be assembled into AOP networks that may aid the prediction of more complex interactions and outcomes resulting from exposure to complex mixtures and/or chemicals with multiple modes of action. These AOP networks then afford the opportunity to integrate and evaluate the potential for impacts associated with nonchemical stressors, in addition to chemical stressors. By considering AOPs and AOP networks associated with important developmental processes, as well as those associated with disease endpoints of concern, mechanistic toxicology information and epidemiology insights can be brought together for model development and analysis of critical knowledge gaps.

A major challenge is to translate AOP frameworks across scales of biological organization (molecules, cells, tissues, populations) and function, while incorporating critical windows of exposure, dose, pharmacodynamics, and pharmacokinetics. Multiscale modeling and simulation is a powerful approach for capturing and analyzing biological information that is inaccessible or unrealizable from traditional

modeling and experimental techniques. For example, virtual tissue models (VTMs) afford the opportunity to develop science without conducting studies in children. By simulating a range of predicted effects, the earliest signs of adversity can be identified, and new testable hypotheses aimed at improving the accuracy of inferences from *in vitro* data. These same modeling approaches can be applied to capture the complexity of children's interactions with the environment in their home, school and community as well as to postulate key environmental determinants of health.

ORD will continue to identify effective strategies for fostering emerging scientific understanding and encouraging application of the latest science to inform Agency decisions. For example, the importance of epigenetic changes, i.e., the alteration of birth outcomes and/or the reprogramming of cells to promote disease susceptibility and metabolic dysfunctions that could occur later in life, is just beginning to be understood. Some of the EPA/NIEHS Children's Centers are currently doing work in this area and further research is needed, using both experimental and epidemiological approaches, to help increase the understanding of the extent to which environmentally-induced epigenetic changes can contribute both to future disease status and to future resilience.

Research Area 3: Methods and models to evaluate early lifestage-specific risks and to support decisions protective of all lifestages

As guidance for incorporating consideration of lifestage specific risks into Agency decisions are implemented, the need to incorporate a wide range of lifestage specific information into workflows and analytical tools to support assessments has increased. Methods and tools are needed to effectively address a growing range of considerations and factors where data may be limited. Priority needs are for:

- Rapid, efficient methods to characterize children's total environments, including the built and natural environments, where pregnant women and children live, learn, and play,
- Rapid, efficient methods for evaluating potential for developmental toxicity Science-based tools to support consideration of critical child-specific vulnerabilities for environmental and health policy decisions that promote and protect children's health.

For example, there is currently only limited information on exposures and exposure factors for infants and children less than 6 years of age. In addition, even when there is information on exposure levels from biomonitoring or other sources, there is little knowledge on the pathways of exposure, i.e., whether the exposure is predominantly from air, food, water, or other sources. Such information remains a critical gap in EPA's Exposure Factors Handbook (U.S. Environmental Protection Agency, 2011), a resource that is widely used across the Agency and by other organizations to conduct chemical risk assessments. Novel, ultra-low burden approaches are required to develop the exposure factor information and data required to support these Agency assessments of risks in early life. There are also important gaps in methods and approaches for characterizing potential exposures associated with the home, school, and community environment required to assess risks associated with real-world exposures to mixtures as well as to characterize potential modifying factors for more holistic decisions and solutions.

Another high priority Agency research need is for continued development and evaluation of assays and testing schemes to identify the potential for developmental toxicity and human-relevance across the full range of critical endpoints. Assays that can be implemented in rapid, cost effective schemes are of

particular priority to facilitate development of data for thousands of chemicals in commerce that have not been evaluated for potential impacts to developmental pathways.

Research Area 4: Translational research and tools to support community actions and decisions

A lifecourse approach to health considers how an individual's current and future health may be affected by the dynamic interaction among social, biological, and environmental influences over time. It underscores the importance of multiple risk and protective influences and considers how the presence or absence of these influences during critical and sensitive stages of development may affect the health of individuals or selected populations (National Research Council, 2011). There is expected to be significant investment by NIH to support public health in vulnerable populations and groups, including children. EPA leadership will be required to enable research that meets targeted needs for translational tools incorporating lifestage- specific considerations to provide local decision makers with the knowledge needed to inform a balanced approach to community cleanup and development. Priority needs are for:

- Translational tools that can be used by community decision makers to access and use quality data sources specific to promote children's healthy development,
- Research related to child-specific impacts of exposure to non-chemical and chemical stressors at the community level.

State, Tribal and local governments make decisions that impact children's health and wellbeing in communities and settings (e.g., schools, daycare facilities, homes) where they live, work and play. In order to optimize child (lifestage)-specific settings, community decision makers need access to information on the health impacts of multiple factors in the built and natural environment that contribute, in positive or negative ways, to children's health, and their importance relative to each other. A lifecourse approach is needed to identify the types of decisions that focus on child- (or lifestage-) specific environments. By taking a lifecourse approach and building such information into decision support tools, community decision makers can optimize features of the built and natural environments so as to reduce (eliminate, prevent) risk and actively promote healthy development and wellbeing.

A. Informing 2016-2019 ORD Research Planning

EPA's Office of Research and Development's (ORD's) National Research Programs (Air, Climate, and Energy; Safe and Sustainable Water Resources; Sustainable and Healthy Communities; Chemical Safety for Sustainability; Human Health Risk Assessment; and Homeland Security - http://www2.epa.gov/epa-research/strategic-research-action-plans) are aligned on the core principle of sustainability and are designed to provide the solutions the Agency and the nation need to meet today's complex environmental and human health challenges. Inevitably, important scientific issues arise that cut across these six programs. Rather than create additional research programs for every cross-cutting issue, ORD is developing Research Roadmaps to clearly identify the science questions and associated research efforts that are ongoing in the six programs. These Roadmaps identify scientific gaps that inform the National Research Programs in the development of their Strategic Research Action Plans. As new, high priority, cross-cutting issues emerge, ORD expects to use this approach to integrate existing research efforts and identify needed work. Specific research products/deliverables are not included in the

Roadmap: these may change as a result of ORD's planning and budgeting each year. However, ORD will use the EPA's website to provide details regarding research products/associated with implementation of this Roadmap. Here we elaborate on the objectives of integrated ORD research in CEH and on the approach for enabling this research through the National Research Programs.

Objective: Apply advanced and emerging science to understand and predict the role of exposure to xenobiotic environmental factors during early life, in the context of important non-chemical stressors, on health impacts across the course of development. Develop tools to address the complexity of CEH and support decisions that promote health and wellbeing of children.

Conceptual Framework

Systems theory provides the required framework for linking exposure science, toxicology, and epidemiology to study, characterize, and make predictions about the complex interactions between children and environmental stressors (both chemical and nonchemical) across the course of development (Figure 3). Multifactorial exposures to individuals, communities, and populations are captured horizontally from left to right (source-to-dose response with feedback), while outcome hierarchy is captured vertically from bottom to top (adverse outcome pathway). Kinetics and dynamics of these complex systems processes are not depicted, but are critical to meet the objective of moving toward development of predictive tools for supporting risk-based decisions.

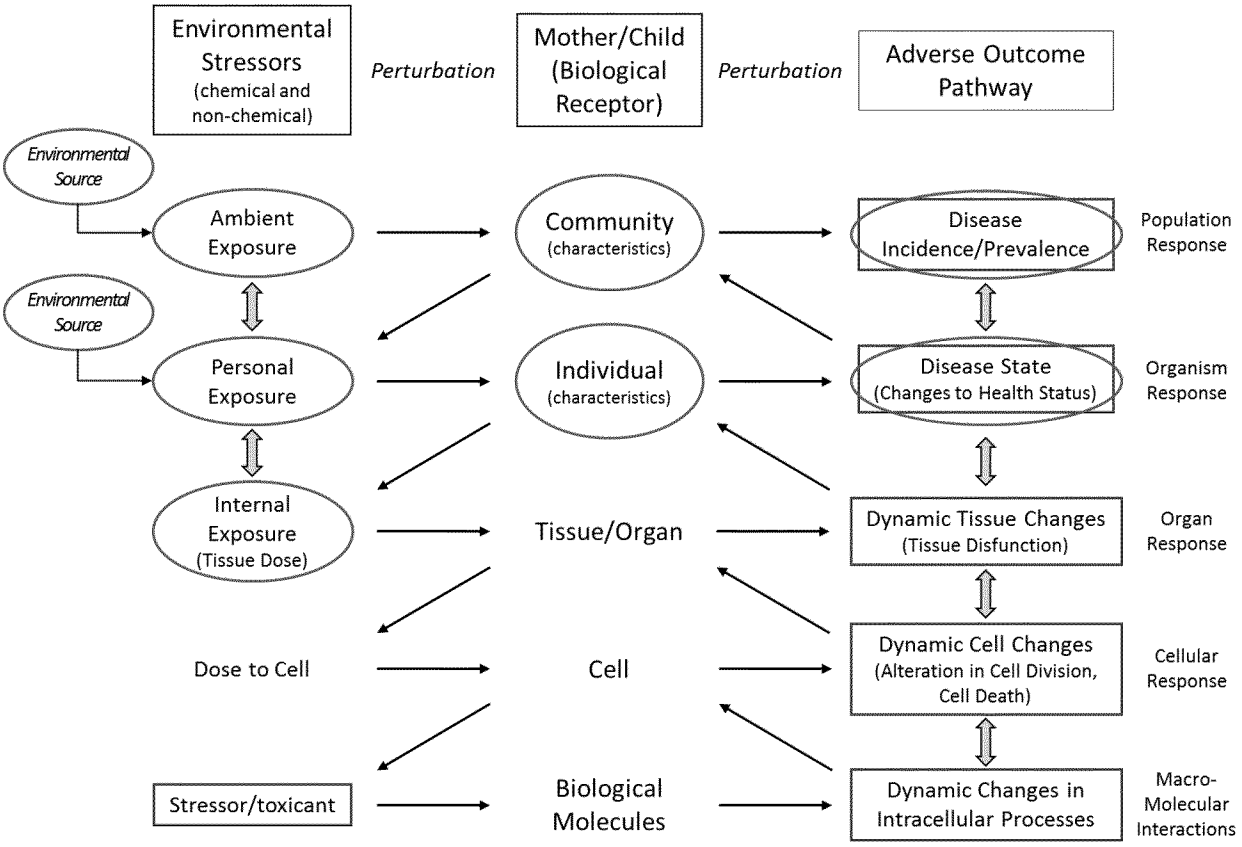


Figure 2. Concept for integrated CEH research in ORD.

The science developed will support consideration of multiple vulnerability and susceptibility factors for risk based decisions. Exposure assessment and risk assessment require population and community-specific information or exposure factors that may vary significantly based on geography and cultural practices. These factors have been reviewed and a framework has been described to facilitate systematic consideration of these contextual factors for exposure and risk assessment (see Table 6) (DeFur et al., 2007).

Table 6. Examples of specific vulnerability factors (DeFur et al., 2007)

Environmental Conditions (habitat quality)		Receptor Characteristics (individual or group quality)	
Location	Noise	Biological factors	Adaptability
Geographic area	Social environment	Genetics	Intensity
Urban	Segregation	Gender	Mood
Rural	Crime	Genetic diversity	Persistence/attention span
Proximity to industrial sites	Chaos	Genetic flux	Distractibility
Proximity to roads and traffic	Conflict	Susceptibility	Sensitivity
Time indoors, time outdoors	Social support	Developmental or lifestage	Activities/behaviors
Quality of setting	Immigration/ emigration	Age	Physical activity
Natural environment	Family or group stability	Population structure	Hygiene
Air quality	Violence	Physical health status	Diet
Water quality	Racism	Low birth weight	Product use
Climate, habitat	Resources	Chronic disease-obesity	Smoking
Built environment	Social capital	Compromised immune function	Substance abuse
Land use	Wealth	Asthma	Religious practice
Housing quality	Employment opportunities	Acute disease-exposure	Social factors
Housing density	Schools	Infection	Race/ethnicity
Occupant density	Medical care	Nutrition	SES
Sanitation	Food availability	Injury	Population size
Traffic density	System complexity and redundancy	Psychologic factors	Diversity
		Mental/emotional health	Number of species
		Depression	Marital status
		Hostility	Educational status
		Poor coping skills	Other
		Temperament	

Conceptual Approach

EPA CEH Research will apply complex systems science to integrate the rapidly expanding body of information on children's environments with advancing insights on developmental processes to inform the understanding of key factors contributing toward health outcomes. This understanding will be translated and tools provided to support Agency decisions that promote and protect children's health and wellbeing.

Studies will be model-driven to direct resources toward filling priority scientific gaps and to facilitate advancement of Agency capacity to be predictive of potential risks. This approach iteratively measures, mines, models, and manipulates (4M's) to extract maximum understanding from extant data and to provide tools that support holistic evaluation of the complex interactions that determine health impacts of early life exposures. To ensure short term impact in support of Agency needs, the scope of the research will be targeted by implementing studies through case examples focused on priority health outcomes and exposures as identified by ORD Program Office Partners through the NRPs.

Measurement includes obtaining multi-dimensional information of the system through a variety of methods including high-throughput data capture. This involves much of the same data capture approaches that have been traditionally performed, but broadens the space through increasing system complexity (e.g., cellular processes, metabolism, protein location, receptor binding, enzyme activation/inhibition, biomarkers of exposure, environmental concentrations) and efficiency (e.g., rapid screening methods requiring fewer materials and increasing output).

Mining includes the organized compilation of the multi-dimensional data into usable databases, and bioinformatics approaches which mine the database to develop plausible relationships providing systems-based hypotheses, including for example, putative AOPs.

Modeling includes developing statistically-based signatures (i.e., metrics) and computational-mechanistic models from the relevant information. These models are complex, nonlinear, and interconnected integrating the data beyond a linear process.

Manipulation includes functional studies to predict system-level behaviors *in silico* and to evaluate model performance. An iterative process of prediction-validation is necessary to refine models in order to adequately represent the human-environment system at important levels of organization, whether the consequences result in normal development and wellbeing or adverse consequences to development and health.

This approach calls for knowledgebase-driven methods to incorporate information from past and current research, compilation of plausible pathways and mechanism of exposure and toxicity, models that can predict whether or not a chemical will elicit an adverse outcome, simulations that can incorporate these models, validation models for checks and balances, and acceptance and integration into current risk assessment paradigms, as well as integrating these data in new ways to evaluate risk.

Application of this common approach to identify the most important environmental factors driving early-life exposures and associated health outcome over the lifecourse will address key scientific gaps required to support the Agency's mission and strategic goals for protecting and promoting children's wellbeing.

Example 1: Birth Outcomes (Vascular VTMs)

The Virtual Tissue Modeling (VTM) project focuses on biologically-driven assembly to enable (*in vitro*) and simulate (*in silico*) key events in an AOP framework with respect to spatio-temporal dynamics in human development. The overall goal is to advance the mechanistic understanding of how chemical disruption of cell lineage, fate and behavior propagates to higher levels of biological organization and adverse developmental outcomes. Genomic and environmental signals act cohesively during successive windows of development. When disrupted, these changes can impact aspects of maternal or filial development leading to an array of adverse birth outcomes (e.g., malformations, low birth weight).

Embryonic vascular network assembly is a complex process characterized by the formation of geometric tubular networks (vasculogenesis). The early pattern is based on differential cell growth, migration and survival along a growth factor (VEGF-A) gradient as well as differential cell adhesion and cell folding that connect the endothelial cell network and create a patent luminal channel, respectively. Subsequent growth and remodeling of the primitive capillary network (angiogenesis) is mediated by invasive angiogenic sprouting induced by local growth factors linked to oxygen tension as well as shear-stress signals following establishment of blood flow (Perfahl et al., 2011; Shirinifard et al., 2009). To understand and predict impacts of chemical exposures on this system, computational systems models have been built that incorporate all of the systems biology framework components (measurement, mining, modeling, manipulation). This provides a good example for how the systems biology approach can be applied to a particular developmental system.

Measurement: Data of chemical-biology perturbations came from the EPA's ToxCast program, as well as from text mining the public literature. A number of ToxCast assays specifically related to the vascular system were selected for incorporation into AOPs and computational simulation models. These assays and targets came from a human primary co-culture cell system with eight cell lineages (e.g., endothelial, peripheral blood, coronary artery smooth muscle, fibroblasts) evaluating protein secretion readouts (e.g., tissue factor, VCAM-1, MCP-1, uPAR, MMPs, TGFb, collagen), cell-free assays evaluating protein binding (e.g., VEGF, endothelin) and enzyme activity (e.g., caspase, ephrin, MMPs, Tie2), and cell-based assays evaluating transcriptional regulation (e.g., RAR, VDR, TGFb). A litany of MeSH terms was developed based on annotated genes, canonical pathways and cellular processes that could be linked to normal and abnormal vasculogenesis and angiogenesis to identify relevant vasculature-related articles and co-annotated concepts and principles.

Mining: Mining techniques combined literature mining integration tools (eLibrary) and bioinformatics approaches for making predictions about putative Vascular Disrupting Compounds (pVDCs). Using the MeSH terms indicated above on the public literature domain limited the articles to 100,000. These articles were organized in a way to assist in finding relevant relationships described in the articles and annotated in the MeSH terms. In the case of angiogenesis, for instance, the relationship between angiogenesis and proteins are captured by extracting co-annotations for neovascularization and proteins. Similarly, chemicals co-annotated with neovascularization are extracted into another sheet and organized by whether the chemical appears from the MeSH annotations to have an adverse effect on neovascularization or to have a therapeutic effect on neovascularization. The protein annotations are further processed to look at co-annotations in the literature which coarsely indicates a biological relationship. Although the exact nature of the relationship is not identifiable from the annotations, the knowledge that two proteins are co-annotated is a helpful starting point for more in depth exploration and further research. These associations are helpful in elucidating AOPs within the modeling section.

Chemicals were identified to be potential vascular disruptors, pVDCs, through identifying and prioritizing the ToxCast HTS assays relevant to vascular development. Six broad classes of assay targets (24 in total) were identified from the HTS assays, including receptor tyrosine kinases (VEGFR2, TIE2), GPCR-based chemokine signals (CXCL10, CCL2) and the GPI-anchored signals from matrix remodeling (PAI1, uPAR) among others. Next, the chemical-assay target activities for each chemical were used to rank the chemicals as least to most likely to affect the developing vasculature system. This provided a list of potential chemicals to pursue in follow-up modeling and confirmation steps across 1060 chemicals in the ToxCast library.

Modeling: AOPs delineate the documented, plausible, and testable processes by which a chemical induces molecular perturbations and the associated biological responses that describe how the

molecular perturbations cause effects at the subcellular, cellular, tissue, organ, whole animal, and population levels of observation. This concept identifies the pathway linking a molecular initiating event (MIE) to an adverse outcome. To identify potential MIEs, the gene ontology (GO) and mammalian phenotype (MP) browsers of the Mouse Genome Informatics database (http://www.informatics.jax.org/) were searched for terms affiliated with the disruption of vascular development. Terms for abnormal vasculogenesis [MP:0001622; 72 genotypes, 73 annotations] and abnormal angiogenesis [MP:0000260; 610 genotypes, 894 annotations] were captured into a table as well as the gene and protein and then both were linked to ToxCast assays. This list had 65 target genes with bona fide roles in vasculogenesis or angiogenesis, 50 of which had evidence of abnormal embryonic vascular development based on genetic mouse models (Knudsen & Kleinstreuer, 2011). The proposed AOP for embryonic vascular disruption is shown in Figure 3.

An integrated understanding of the mechanisms and key events underlying embryonic vascular disruption requires a modeling framework to link relevant information about molecular pathways and cellular processes with the kinetics and dynamics of the system that describe the interactions and functioning of those elements. A systems biology approach is required to extend traditional conceptual linear models into computational models that are ideally quantitative or predictive. In building a simulation model of this process, each simulated cell in the model, like a biological cell, has an inherent capacity to process local information from the microenvironment and respond according to its own genetic blueprint or history. The key molecular players and cellular behaviors of concern were identified via the eLibrary, AOP framework, and ToxCast assay data. By incorporating these data and critical pathways and processes (e.g., extracellular matrix remodeling, chemokine pathways, growth factor signaling), the model can test certain hypotheses on cell signaling interactions and emergent vessel network topologies following chemical disturbance of specified growth factors, cell-surface receptors, and breakdown of the extracellular matrix. Discrete cellular behaviors (growth, adhesion, proliferation, apoptosis, chemotaxis) and parameters (growth factor diffusion, decay, secretion and uptake rates and cell size, motility, growth rate) were programmed into the simulation. Model outputs (cell number, angiogenic index, average vessel length/diameter, number of branching points) were compared to histological data for accurate representation.

Manipulation: Confirmation studies for the AOP and simulation model on vascular development included several anti-angiogenic reference compounds: 5HPP-33 (thalidomide analogue), TNP-470 (Wnt inhibitor), PTK787 (VEGFR2 inhibitor), and AG1478 (EGFR inhibitor). The 5HPP-33 reference compound was confirmed active in ToxCast Phase II assays across the AOP signature. In collaboration with scientists at the DOW Chemical company, 5HPP-33 and TNP-470 were shown to interfere with microvessel outgrowth in aortic explant assay and caused lethality (5HPP-33 ≥ 15μM) and malformations (TNP-470 ≥ 0.25 μM) in rat whole embryo culture. Computer simulation with 5HPP-33 predicted similar exposure-related morphological effects. RNA-Seq analyses were proposed to aid in understanding the specificity of the vasculogenesis-disruption mechanisms and allow identification of novel gene targets perturbed following chemical exposure. RNA-Seq analysis conducted on rat embryos (GD10) exposed to 5HPP-33 and TNP-470 in vitro revealed concentration-dependent effects on vasculogenesis genes (i.e., VCAM1, TNF, CASP8, HIF1A, AHR). These studies provide evidence that the science is correctly understood within the context of this research and that the predictions are plausible.

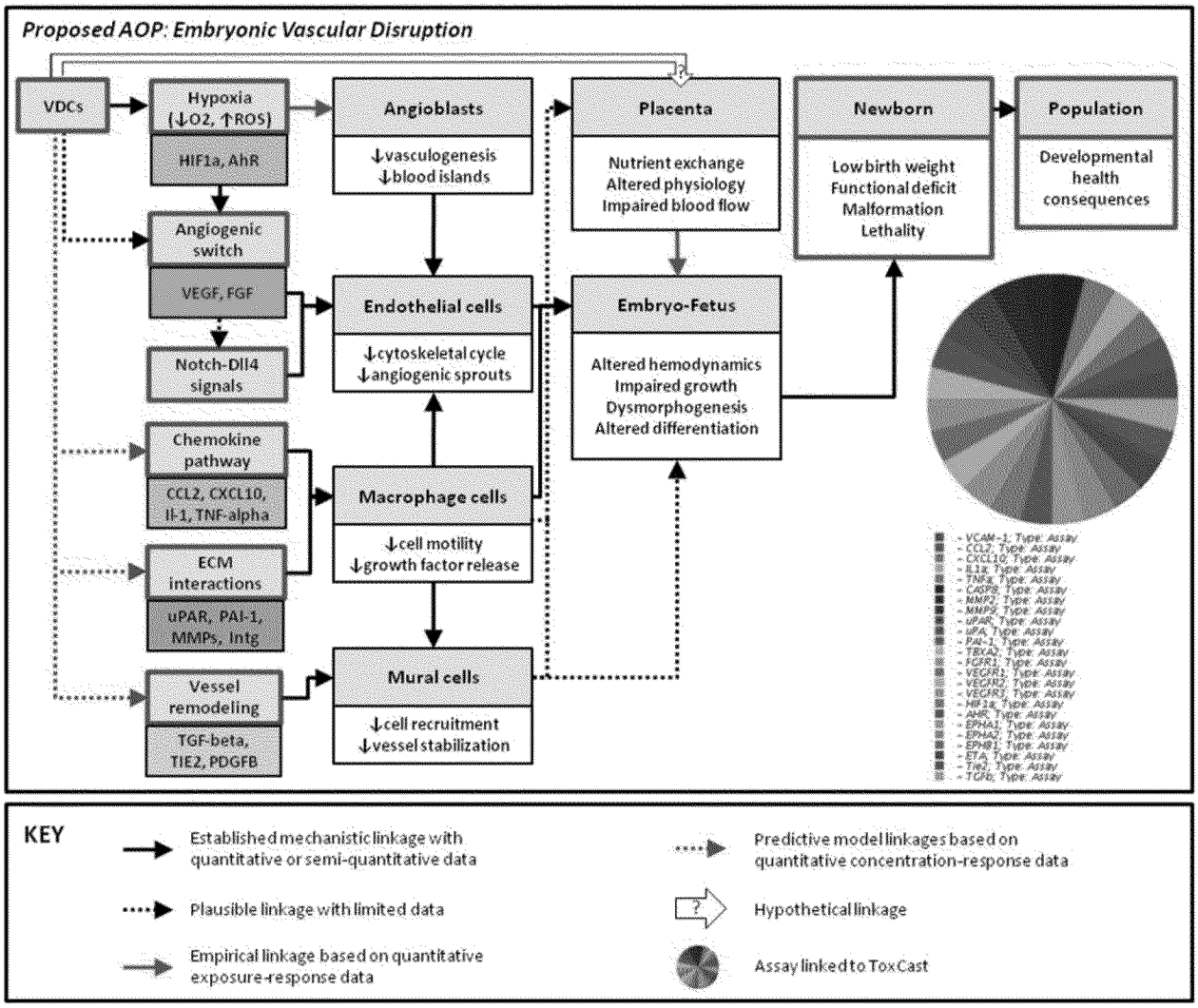


Figure 3. Proposed AOP for embryonic vascular disruption.

Example 2: Asthma (MICA Study)

Despite recent evidence suggesting that the very large increase in asthma incidence and prevalence observed in recent years may be slowing (Akinbami, Mooreman, & Liu, 2011), the global burden of this complex disease remains at an all-time high. More than 20 million Americans have asthma, including approximately 7 million children under the age of 18. The cost of treating asthma in children under 18 in the U.S. is estimated at $3.2 billion per year. Prevalence of asthma in low income and minority children in the United States is disproportionately higher (Akinbami et al., 2011; von Mutius & Hartert, 2013).

The Mechanistic Indicators of Asthma (MICA) study was designed to investigate whether genomic data (blood gene expression), viewed together with a spectrum of exposure, effects, and clinical and

susceptibility markers can increase the sensitivity required to define exposure-response-effects relationships and provide mechanistic insight for further hypothesis generation and testing. As such, this study provides an example of how a systems biology approach can support a more holistic understanding of the multifactorial etiology of environmental disease (Gallagher et al., 2011; George et al., 2015).

Measurement: A nested case-control cohort of 205 non-asthmatic and asthmatic children, (9-12 years of age), from Detroit, Michigan were recruited. The integrated study design and framework for MICA is shown in Figure 4. The MICA design focuses on environmental exposures, susceptibility, asthma and other health measures, including risk factors associated with obesity and cardiovascular disease. Information on a wide range of risk factors relevant to asthma and asthma exacerbations were characterized through collection of exposure metrics, lung function tests and biological and clinical indicators measured in blood, urine, and fingernails. The study includes environmental measures (indoor and outdoor air, vacuum dust), biomarkers of exposure (cotinine, metals, total and allergen specific Immunoglobulin E, polycyclic aromatic hydrocarbons, volatile organic carbon metabolites) and clinical indicators of health outcome (immunological, cardiovascular and respiratory). In addition, blood gene expression and candidate SNP analyses were conducted. Selected measurements are highlighted in Figure 4.

Mining: Traditional analysis of complex disease considers one domain of data at a time to identify associations between biomarkers or bioindicators and disease outcomes. The commonly employed methodologies used require a clearly defined phenotype representative of multiple underlying disease processes for traditional supervised methods or a disease clearly identifiable by genomic or clinical data for traditional unsupervised methods, neither of which is true of complex disease. The large data sets that are now widely available can be mined to define novel, mechanistically distinct disease subtypes (endotypes) in a completely data-driven manner. Approaches for maximizing the discovery potential of these data sets are still an area of significant research. Alternative approaches for mining the MICA data were evaluated (e.g., Student's t-test, single data domain clustering and the Modk-prototypes algorithm). To best exploit strengths and limitations of the MICA data, a novel multi-step decision tree-based method was developed to define endotypes. This new method gave the best segregation of asthmatics and non-asthmatics, and it provided easy access to all genes and clinical covariates that distinguish the groups (Williams-DeVane et al., 2013).

Modeling: As noted above, gene expression data were combined with hematologic, immunologic, and cardiopulmonary covariates to define mechanistically distinct subtypes (or endotypes). A novel method was used to integrate the clinical covariate data with gene expression resulting in a recursive partitioning tree that segregated individuals according to their asthma status. The resulting tree model assembled asthmatic subjects into purely data driven endotypes. These endotypes were consistent with previous classifications, though the data suggest multiple mechanistically distinct neutrophilic subtypes. Functional characterization of the genes and associated covariates revealed a complex interaction among Th2 mediated lung inflammation, heightened systemic innate immune response, and potentially metabolic syndrome in discriminating asthma endotypes. These findings support a prominent role for systemic inflammation due to heightened innate immune responsiveness across the asthma syndrome and suggest that new biomarkers are needed to better classify mechanistically distinct neutrophilic endotypes.

Manipulation: Characteristics of the data-driven derived endotypes from this study are consistent with previously published endotypes based solely on clinical diagnostic criteria, but this data-driven method provides mechanistic understanding that is not possible when using established clinical markers alone.

One theme that emerges from this analysis is the interplay between innate and adaptive immune responses across endotypes. Results also suggest a role for broad systemic inflammation in addition to the localized hyperreactivity in the lung as a major driver for asthma. The findings of this data-driven mining and modeling approach are consistent with studies demonstrating that weight loss improves asthma symptoms without significant changes in markers of airway inflammation. Of note, body mass index (BMI) alone is not a predictor of asthma in the MICA study, in contrast with other recent studies; this may be because MICA looks at asthma prevalence in children rather than correlates of asthma onset. The MICA study, among others, putatively identifies underlying mechanisms linking obesity and asthma through systemic inflammation related to metabolic syndrome and increases the relevance and understanding of clinical findings.

The result of applying this holistic approach to the study of asthma in children is a better understanding of the various asthma endotypes and a scientifically defensible foundation for the evaluation of the many environmental factors influencing each mechanistically distinct endotype. Non-eosinophilic asthmatics likely fall into multiple mechanistically distinct subgroups or endotypes. Exacerbation of asthma by obesity and metabolic syndrome likely occurs through enhanced systemic inflammation, which will not be detected by biomarkers reliant on airway inflammation.
Asthma biomarkers reliant on airway inflammation may miss endotypes driven by systemic inflammation. The increasing incidence of asthma due to the rise in obesity will expand the proportion of these endotypes.

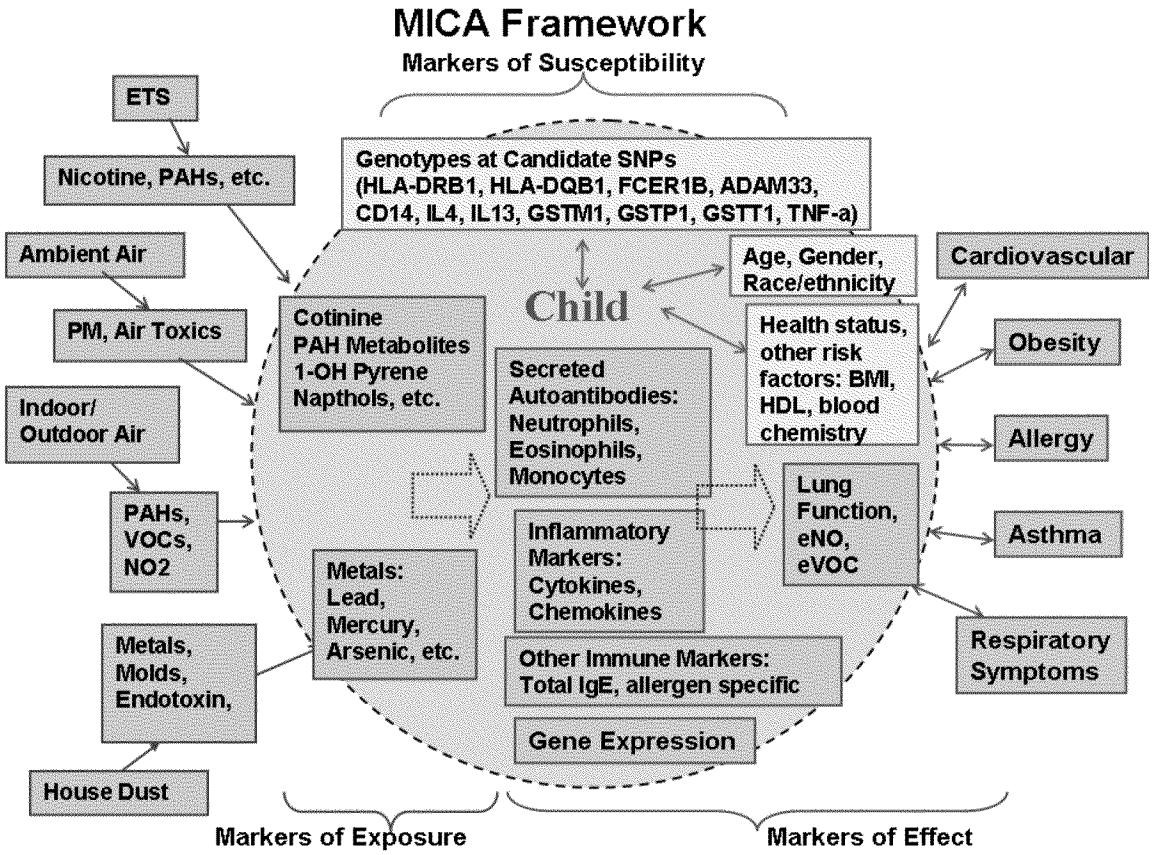


Figure 4. The overall MICA study design includes exposure, biomarkers of exposure, clinical indicators, genomic data (blood gene expression and SNP) and health status indicators.

Example 3: The Future of Cross-Cutting CEH Research

The traditional risk-based assessment paradigm supports decisions to minimize adverse impacts associated with environmental exposures. Clearly, removing chemical/pollution stressors is a necessary and essential component of children's health protection. Community planning and development decisions are designed from the holistic perspective of both minimizing risks while at the same time providing an environment that supports and promotes healthy (optimal) child development. Such a goal is an inherent property of sustainability. To support this goal, novel methods are required to incorporate and consider the complexity associated with these decisions and to compare alternatives and evaluate outcomes.

For example, the same agent-based modeling tools used by the ORD Virtual Tissues Modeling project to simulate how chemical perturbations at the cellular level propagate to higher levels of biological organization can potentially be applied to simulate population level interactions of children in a community. It has been suggested that health behavior research is a candidate for application of complex systems modeling approaches to address empirical questions that cannot be addressed using the regression approaches common to the field of social epidemiology (Galea, Hall, & Kaplan, 2009). Similarly, these approaches could provide the capacity to integrate the vast array of information required to computationally test and evaluate community-level interventions and public-policy decisions designed to improve CEH. By designing cross-cutting ORD research to extend these approaches across all levels of organization, important gaps in data and understanding can be efficiently identified for targeted study and data collection. The conceptual research framework and approach described in these three examples, implemented through case examples of high priority to ORD program office and regional partners, will facilitate integrated research required to support holistic and sustainable decisions in support of CEH.

VI. Summary

CEH research is conducted by the EPA to improve the scientific understanding required to support: regulatory decisions protective of children's health now and in the future; community decisions that protect and promote children's health across generations; and, ecological decisions that provide sustainable healthy environments for children. The overarching goal for EPA's CEH research program is to provide the Agency and others with the information needed to incorporate consideration of early lifestage susceptibility and vulnerability into decision making.

EPA's CEH research is designed to address four priority research areas: 1) knowledge infrastructure to provide early lifestage-specific data and information; 2) systems (biological) understanding of the relationship between environmental exposures and health outcomes across development; 3) methods and models fit for purpose to evaluate early lifestage-specific risks and to support decisions protective of all susceptible and vulnerable early lifestages; 4) translational research and tools fit for purpose to support community actions and decisions.

EPA is currently carrying out research in each of these four areas and plans to build on this research as it plans for the future. EPA will continue to partner with other Federal agencies and independent organizations to further CEH research. Future research will apply complex systems science to integrate the rapidly expanding body of information on children's health. This information will be translated into tools and databases that will support Agency decisions that promote and protect children's health and wellbeing. Model-driven studies will be used to direct resources toward filling priority scientific research gaps and to advance the Agency goals of protecting human health and the environment.

VII. References

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